National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Vulvar Cancer

Version 1.2025 — February 10, 2025

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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Discussion

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NCCN Guidelines Panel Disclosures

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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Updates in Version 1.2025 of the NCCN Guidelines for Vulvar Cancer from Version 4.2024 include:

Vulvar Cancer (Squamous Cell Carcinoma and Adenocarcinoma)
General:
• The algorithm title revised to: Vulvar Cancer *(Squamous Cell Carcinoma and Adenocarcinoma)*

VULVA-1
• The following revisions were made due to the pathway for "Cutaneous vulvar melanoma or Mucosal vulvovaginal melanoma" moving to pages VM-1 and VM-2:
  ▸ Workup: Bullet removed, Consider somatic mutational testing for vulvar melanoma and mucosal vulvovaginal melanoma as clinically indicated (ie, BRAF, KIT).
  ▸ Footnote a revised: Principles of Pathology (VULVA-A). ~~If vulvovaginal melanoma is suspected, see Principles of Biopsy and Pathology (ME-B) in the NCCN Guidelines for Melanoma: Cutaneous.~~
  ▸ Footnote b revised: Principles of Imaging (VULVA-B). ~~If vulvovaginal melanoma is suspected, See Principles of Imaging (ME-D) in the NCCN Guidelines for Melanoma: Cutaneous.~~

VULVA-2
• Stage IA (≤1 mm invasion); Primary Treatment revised: Simple partial vulvectomy *(preferred)*

VULVA-4
• Footnote p is new: EBRT only if patient is not suitable for complete inguinofemoral lymphadenectomy.

VULVA-5
• Primary Treatment; Inguinofemoral lymphadenectomy; Negative LNs: Revised, EBRT + concurrent chemotherapy to primary tumor (± selective inguinofemoral LN coverage ± *selective pelvic lymph node coverage*)

VULVA-6
• This page was extensively revised, including:
  ▸ Evaluation of Response to EBRT + Concurrent Chemotherapy
    ◊ Top pathway
      – Clinically negative for residual tumor at primary site and nodes pathway: The option to "Consider biopsy of tumor bed to confirm pathologic complete response (pCR)" was removed from this pathway.
    ◊ Bottom pathway
      – Revised language: Clinically ~~positive~~ *suspicious* for residual tumor at primary site and/or nodes *at least 3 months after completion of treatment*
      – *Consider biopsy* added as an option.
  ▸ Footnote b added: See Principles of Imaging (VULVA-B)
  ▸ Footnote q revised: Consider pelvic exenteration for select cases ~~with a central recurrence~~. (Also for VULVA-9)
  ▸ Footnote removed: No sooner than 3 months from completion of treatment.

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Updates in Version 1.2025 of the NCCN Guidelines for Vulvar Cancer from Version 4.2024 include:

Vulvar Cancer (Squamous Cell Carcinoma and Adenocarcinoma)

VULVA-8

- Surveillance
  - 5th bullet revised: ~~Patient education regarding symptoms of potential recurrence and vulvar dystrophy, periodic self-examinations, lifestyle, obesity, exercise, sexual health (including vaginal dilator use and lubricants/moisturizers), smoking cessation, nutrition counseling, and~~ *Clinical evaluation and management of* potential long-term and late effects of treatment (Also see *Principles of Gynecologic Survivorship (VULVA-F)*, NCCN Guidelines for Survivorship and NCCN Guidelines for Smoking Cessation)
- Footnote u revised: ~~Principles of Gynecologic Survivorship (VULVA-F).~~ *Patient education should include symptoms of potential recurrence and vulvar dystrophy, periodic self-examinations, lifestyle, obesity, exercise, sexual health (including vaginal dilator use and lubricants/moisturizers, local estrogen and hormone therapy for menopause), smoking cessation, and nutrition counseling*.

VULVA-9

- Site of Recurrence revised: Vulva-confined recurrence ~~(nodes clinically negative)~~, not previously irradiated *(nodes clinically negative)*
  - EBRT ± brachytherapy ± concurrent chemotherapy changed to EBRT ± brachytherapy + *concurrent chemotherapy*
- Footnote i added: The management of positive margins for HSIL (noninvasive disease) should be individualized.

VULVA-10

- 2nd column; Bottom pathway revised: ~~Multiple pelvic nodes or~~ Distant metastasis or Prior pelvic EBRT
- Therapy for Recurrence, No prior EBRT: EBRT ± concurrent chemotherapy changed to EBRT + *concurrent chemotherapy*

VULVA-A 2 of 4

- Pathologic Assessment for Squamous Cell Carcinoma
  - Additional molecular testing and biomarkers is a new bullet
    - ◊ Sub-bullets revised
      - – Recommend ancillary testing to determine HPV status either by p16 IHC or RNA *sequencing or HPV* in situ hybridization *(ISH) if available,* or DNA sequencing
      - – Recommend p53 IHC to determine p53 status *in HPV-negative tumors (NGS acceptable alternative)*
    - ◊ New sub-bullets added
      - – Consider programmed death ligand 1 (PD-L1) testing for patients with recurrent, progressive, or metastatic disease
      - – HER2 IHC testing (with or without reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) is recommended for advanced or recurrent/metastatic disease.
      - – Consider comprehensive molecular profiling by an FDA-approved assay, or a validated test performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory including at least mismatch repair (MMR)/microsatellite instability (MSI), tumor mutational burden (TMB), and NTRK testing for predicting rare pan-tumor targeted therapy opportunities.
    - ◊ Bullets removed and recommendations incorporated into the new arrow sub-bullets noted above
      - – Consider mismatch repair (MMR)/microsatellite instability (MSI), programmed death ligand 1 (PD-L1), and/or NTRK gene fusion testing for patients with recurrent, progressive, or metastatic disease
      - – Consider tumor mutational burden (TMB) testing as determined by an FDA-approved assay, or a validated test performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory

CONTINUED

Updates in Version 1.2025 of the NCCN Guidelines for Vulvar Cancer from Version 4.2024 include:

Vulvar Cancer (Squamous Cell Carcinoma and Adenocarcinoma)

VULVA-B

- Follow-up/Surveillance; 2nd bullet revised: Consider FDG-PET/CT *and/or pelvic MRI* at 3–6 months to assess treatment response after definitive primary treatment.

VULVA-D 2 of 5

- This section was extensively revised including:
  - Treatment information ~~3D-Conformal/Anterior-Posterior/Posterior-Anterior (AP/PA) Fields~~
    - Target Volumes
      - 1st sub-bullet revised: The target is best defined by both physical examination and CT-based treatment planning; contouring of the target structures is recommended. *Radio-opaque markers should be placed on key landmarks at the time of simulation to assist in definition of the primary target volume*.
      - New sub-arrow bullets added:
        - MRI and/or PET imaging may be fused with the planning CT to aid in the delineation of gross disease. Consensus guidelines for clinical target volume (CTV) definition have been developed and are recommended when developing a treatment plan.
        - IMRT is recommended for better dose delivery to target and sparing of target, with 2D/3D technique reserved for urgent/emergent treatment starts with prompt transition to IMRT in definitive cases, or for palliative treatment
    - New bullet added: "Indications"
      - 1st sub-bullet revised: *Postoperative* indications for treating the primary site include close/positive margin, LVSI, and >5-mm depth of invasion...
      - New sub-bullet added: In both the locally advanced and postoperative settings, especially when there are ≥2 LNs pathologically positive, the bilateral inguinal and pelvic lymphatic regions are typically included in the radiotherapy CTV.
      - 4th sub-bullet; 1st diamond sub-bullet revised: "...is recommended regardless of size of LN metastasis. *If the single positive node is ≥2 mm, adjuvant RT alone to 50 Gy is inferior to inguinofemoral lymphadenectomy. Therefore, in these cases, consider adding chemotherapy or increasing radiation dose to 54–60 Gy or both.*

VULVA-D 4 of 5

- Dosing Prescription Regimen
  - 1st bullet revised: "...coverage of tissues at risk for tumor involvement. *IMRT is preferred over 3D-CRT to reduce dose to normal tissues and to allow for dose escalation."*
  - New bullet added: High recurrence rates have been noted with 50 Gy alone for >2 mm of nodal involvement, or ECE; dose escalation to 54–60 Gy and/or concurrent systemic therapy, preferably on the GROINS-V III protocol, can be considered.

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Updates in Version 1.2025 of the NCCN Guidelines for Vulvar Cancer from Version 4.2024 include:

Vulvar Cancer (Squamous Cell Carcinoma and Adenocarcinoma)

VULVA-D 5 of 5

- New references added
  - Gien LT, Slomovitz B, Van der Zee A, Oonk M. Phase II activity trial of high-dose radiation and chemosensitization in patients with macrometastatic lymph node spread after sentinel node biopsy in vulvar cancer: GROningen INternational Study on Sentinel nodes in Vulvar cancer III (GROINSS-V III/NRG-GY024). Int J Gynecol Cancer 2023;33:619-622.

VULVA-E 1 of 2

- Chemoradiation
  - Preferred Regimens revised: Carboplatin if ~~patient is~~ cisplatin intolerant
  - Other Recommended Regimens updated:
    - ◊ Cisplatin/gemcitabine added
    - ◊ 3rd bullet revised: If *single-agent* cisplatin or carboplatin are unavailable
- First-Line Therapy
  - Preferred Regimens
    - ◊ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab added
    - ◊ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab added
    - ◊ Carboplatin/paclitaxel/bevacizumab changed from category 2B to category 2A
- Second-Line or Subsequent Therapy
  - Useful in Certain Circumstances (Biomarker-directed therapy); *NTRK* gene fusion-positive tumors: Repotrectinib added as an option
- Footnotes were revised as follows:
  - Footnote b is new: *An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.*
  - Footnote d is new: Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.
  - Footnote f revised: "For the treatment of patients with unresectable or metastatic TMB-H [≥10 mutations/megabase (mut/Mb)] tumors~~, as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory~~, that have progressed..."
  - Footnote g revised: Recommended for disease progression on or after chemotherapy in patients whose tumors express PD-L1 (combined positive score [CPS] ≥1) ~~as determined by an FDA-approved assay or a validated test performed in a CLIA-certified laboratory~~.
  - Footnote h is new: Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
  - Footnote i is new: NTRK-positive tumors that are naive to prior NTRK-targeted therapy or have progressed on prior NTRK therapy.
  - Footnote removed: An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

CONTINUED

Updates in Version 1.2025 of the NCCN Guidelines for Vulvar Cancer from Version 4.2024 include:

Vulvar Cancer (Squamous Cell Carcinoma and Adenocarcinoma)
VULVA-E 2 of 2
- New references added:
  - Horowitz NS, Deng W, Peterson I, et al. Phase II trial of cisplatin, gemcitabine, and intensity-modulated radiation therapy for locally advanced vulvar squamous cell carcinoma: NRG Oncology/GOG Study 279. J Clin Oncol 2024:42;1914-1921.
  - Solomon B, Drilon A, Lin JJ, et al. Repotrectinib in patients with NTRK fusion-positive advanced solid tumors, including non-small cell lung cancer: update from the phase 1/2 TRIDENT-1 trial. Poster presented at the European Society for Medical Oncology Congress; October 20–24, 2023; Madrid, Spain.

Vulvar and Vulvovaginal Melanoma
VM-1
- Clinical Presentation; Revised: ~~Confirmed~~ Cutaneous vulvar melanoma
- Column header revised: ~~Additional~~l Workup
  - New Workup bullets added
    - ◊ H&P
    - ◊ Biopsy, pathologic review
    - ◊ EUA cystoscopy or proctoscopy as indicated
    - ◊ Consider somatic mutational testing for vulvar melanoma and mucosal vulvovaginal melanoma as clinically indicated (ie, BRAF, KIT)
- Cutaneous vulvar melanoma
  - Resectable
    - ◊ Stage II; Adjuvant Treatment
      - – If negative SLNB pathway: *See Adjuvant Treatment (ME-3) in the NCCN Guidelines for Melanoma: Cutaneous* was added
      - – If positive SLNB pathway
        - ▪ Systemic therapy and/or RT or Observation removed as options
        - ▪ *See Adjuvant Treatment (ME-5) in the NCCN Guidelines for Melanoma: Cutaneous* was added
    - ◊ Stage III; Primary Treatment
      - – *Consider Neoadjuvant Treatment (ME-6) in the NCCN Guidelines for Melanoma: Cutaneous* added as an option
      - – *See Adjuvant Treatment (ME-6) in the NCCN Guidelines for Melanoma: Cutaneous* was added
- Footnote c is new: See Principles of Molecular Testing (ME-C) in the NCCN Guidelines for Melanoma: Cutaneous. (Also for VM-2)

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VM-2
- Clinical Presentation; Revised: ~~Confirmed~~ Mucosal vulvovaginal melanoma
- Column header revised: ~~Additional~~l Workup
  - New Workup bullets added
    - ◊ Biopsy, pathologic review
    - ◊ EUA cystoscopy or proctoscopy as indicated
    - ◊ Consider somatic mutational testing for vulvar melanoma and mucosal vulvovaginal melanoma as clinically indicated (ie, BRAF, KIT)
- Primary Treatment; Unresectable/Residual disease
  - Clinical trial (preferred) removed as an option
  - Recommendation revised: Systemic therapy ~~and/or~~ ± ~~Primary~~ RT

VM-3
- Follow-up/Surveillance
  - 1st bullet; 1st arrow sub-bullet regarding groin nodal ultrasound for stage ≥ IB revised: every ~~4–6~~ *3–6* months for first 2 years
  - 2nd bullet;
    - ◊ 1st arrow sub-bullet revised: CT scan every ~~4–12~~ *3–12* months
    - ◊ 2nd arrow sub-bullet revised: FDG-PET/CT particularly in cases of high-risk disease every ~~4–12~~ *3–12* months
  - 3rd bullet revised: " See Follow-up recommendations (~~ME-9 and~~ ME-10 *and ME-11*) in the NCCN Guidelines for Melanoma: Cutaneous

VM-A
- This section was extensively revised and reformatted to include separate radiation sections for vulvar melanoma and vulvovaginal melanoma.

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Vulvar Cancer(Squamous Cell Carcinoma and Adenocarcinoma)

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WORKUP

- History and physical (H&P)
- Complete blood count (CBC)
- Biopsy, pathologic review[a]
- Liver function tests/renal function studies
- Imaging[b] as needed for delineating extent of tumor or for treatment planning
- Examination under anesthesia (EUA) cystoscopy or proctoscopy as indicated
- Smoking cessation and counseling intervention if indicated (NCCN Guidelines for Smoking Cessation)
- Consider cervical human papillomavirus (HPV) and cytology testing
- Consider HIV testing[c]
- For patients with vulvar cancer who are older, also see the NCCN Guidelines for Older Adult Oncology

CLINICAL STAGE[a]

Squamous cell carcinoma (SCC)[d] (or adenocarcinomas)

- Early stage (Stage I and select Stage II) → **Primary Treatment** (VULVA-2)
- Locally advanced (Unresectable without removing proximal urethra/ bladder/anus) → **Primary Treatment** (VULVA-5)
- Metastatic disease beyond pelvis → **Primary Treatment** (VULVA-7)

[a] Principles of Pathology (VULVA-A).
[b] Principles of Imaging (VULVA-B).
[c] Consider HIV testing, especially in younger patients suspected of having SCC of the vulva or other HPV-related disease. Patients with vulvar cancer and HIV should be referred to an HIV specialist and should be treated for vulvar cancer as per these guidelines. Modifications to cancer treatment should not be made solely on the basis of HIV status.
[d] Histologic high-grade squamous intraepithelial lesion (HSIL; formerly defined as carcinoma in situ [CIS] and incorporates vulvar intraepithelial neoplasia 2 and 3 [VIN2/3]) can be treated with wide local excision.

Note: All recommendations are category 2A unless otherwise indicated.

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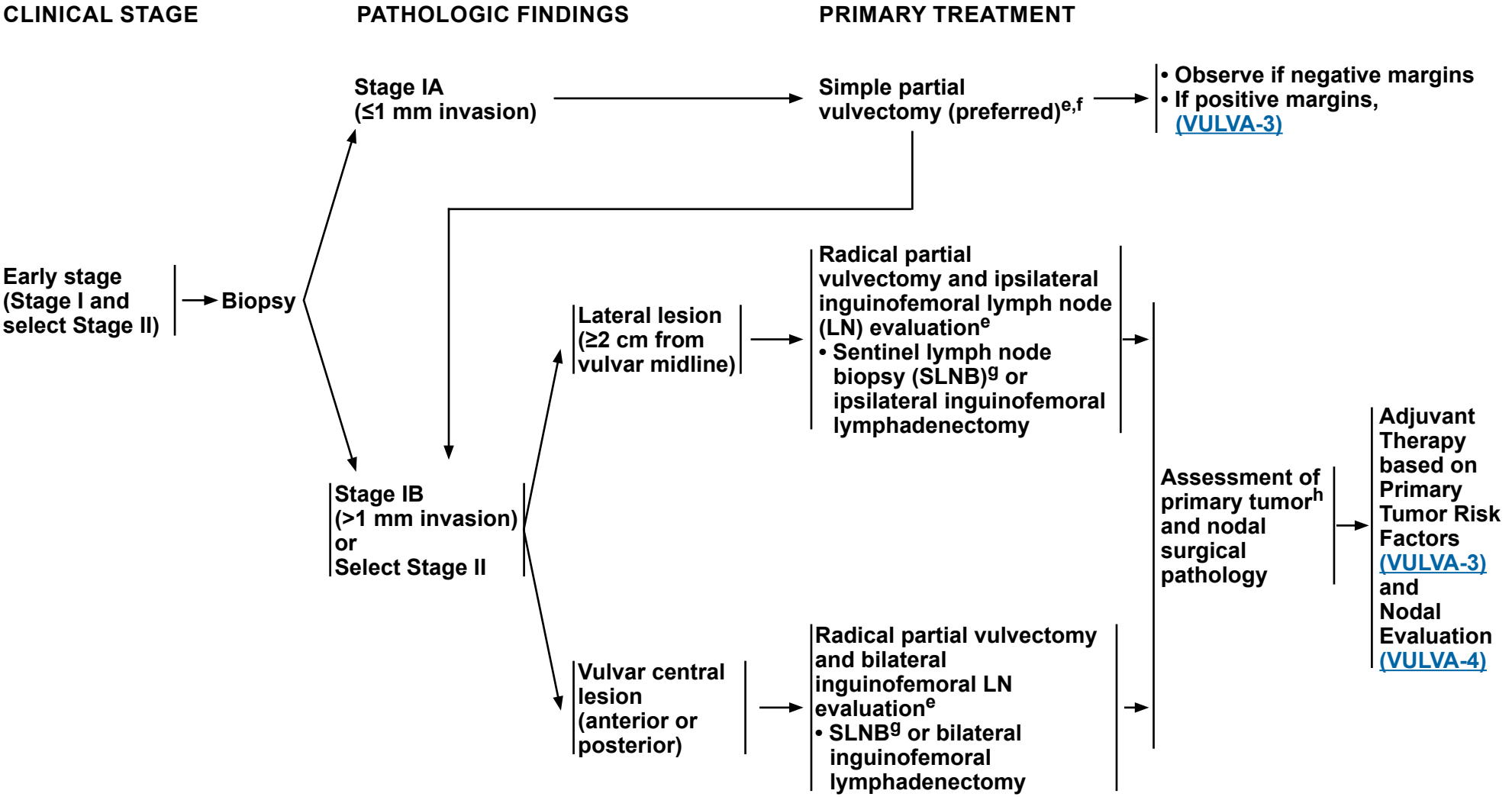
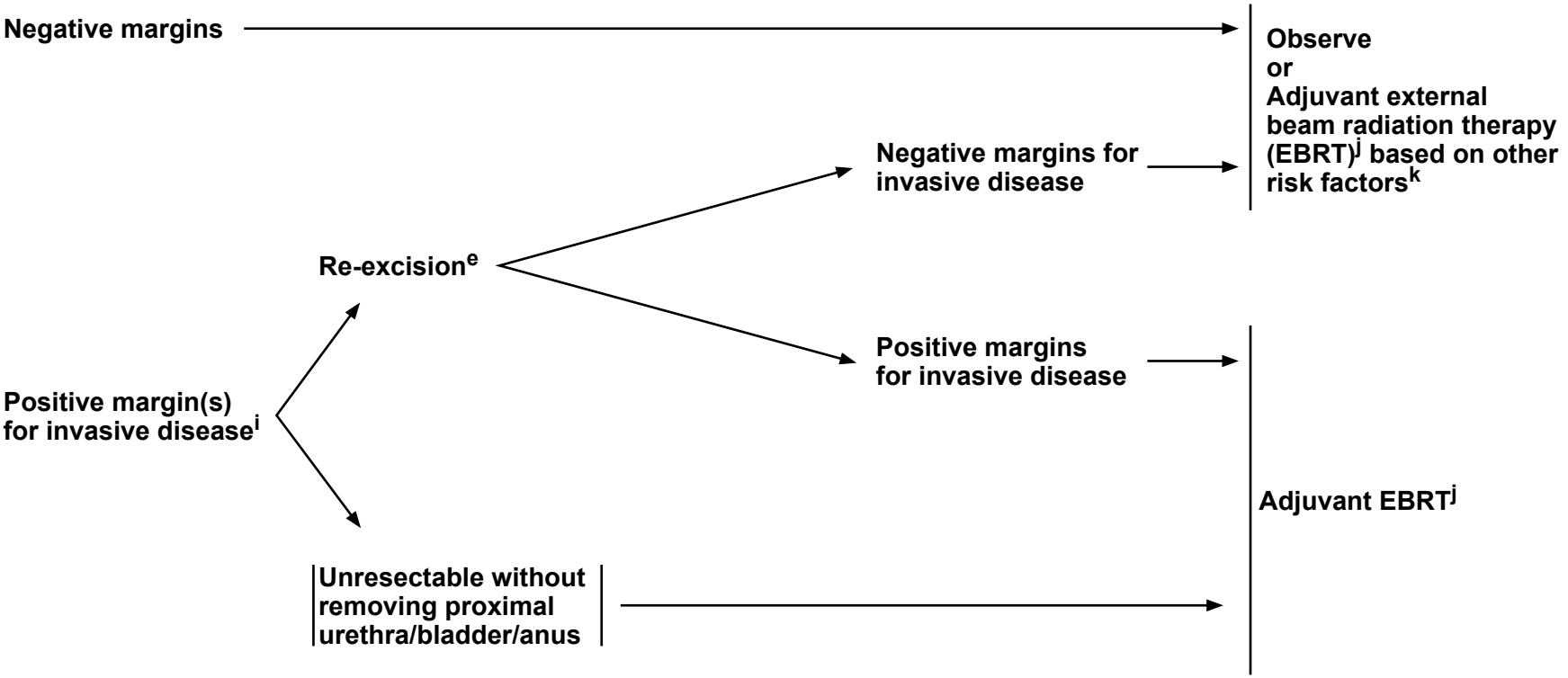


e Principles of Surgery (VULVA-C).
f If partial superficial vulvectomy pathology reveals tumor in aggregate of ≥1 mm invasion, then additional surgery may be warranted.
g Inguinofemoral lymphadenectomy is required on side(s) where sentinel nodes are not detected.
h Principles of Surgery: Tumor Margin Status (VULVA-C 1 of 6).

Note: All recommendations are category 2A unless otherwise indicated.

PRIMARY TUMOR RISK FACTORS

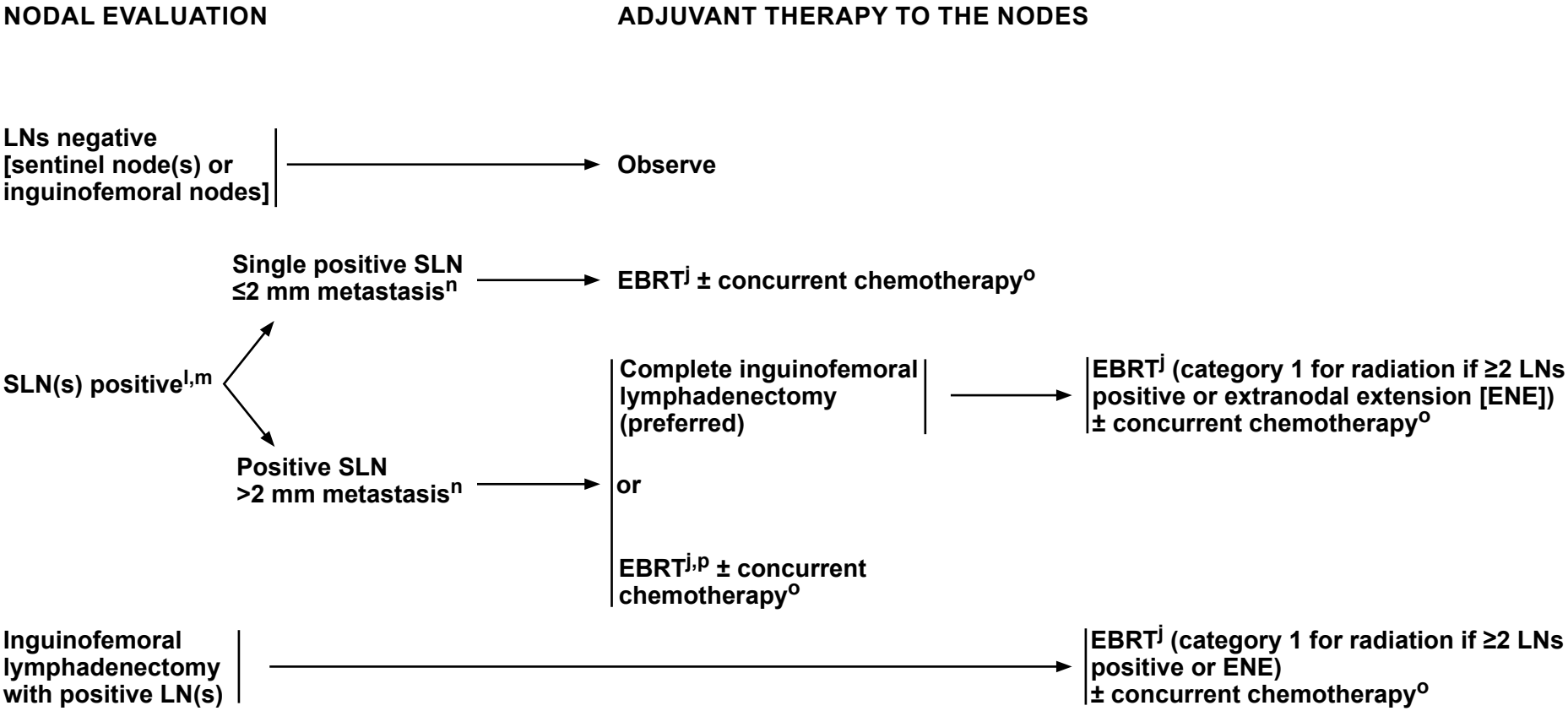
ADJUVANT THERAPY TO THE PRIMARY SITE



Surveillance (VULVA-8)

[e] Principles of Surgery (VULVA-C).
[i] The management of positive margins for HSIL (noninvasive disease) should be individualized.
[j] Principles of Radiation Therapy (VULVA-D).
[k] Other primary risk factors include: close tumor margins, lymphovascular invasion (LVSI), tumor size, depth of invasion, and pattern of invasion (spray or diffuse). Nodal involvement (as an indicator of LVSI) may also impact selection of adjuvant therapy to the primary site.

Note: All recommendations are category 2A unless otherwise indicated.



[j] Principles of Radiation Therapy (VULVA-D).
[l] If ipsilateral groin is positive, the contralateral groin should be evaluated. In select cases of a single, small-volume, unilateral, positive inguinal node with a well-lateralized small primary tumor and depth of invasion ≤5 mm and with a clinically negative contralateral groin examination, a contralateral inguinofemoral lymphadenectomy or radiation may be omitted (Gonzalez Bosquet J, et al. Gynecol Oncol 2007;105:742-746).
[m] Principles of Surgery: Inguinofemoral Sentinel Lymph Node Biopsy (VULVA-C 4 of 6).
[n] The size of 2 mm is used to inform treatment selection/management and the 5-mm cutoff is used for staging. See Principles of Pathology (VULVA-A).
[o] Systemic Therapy (VULVA-E).
[p] EBRT only if patient is not suitable for complete inguinofemoral lymphadenectomy.

Note: All recommendations are category 2A unless otherwise indicated.

Surveillance (VULVA-8)

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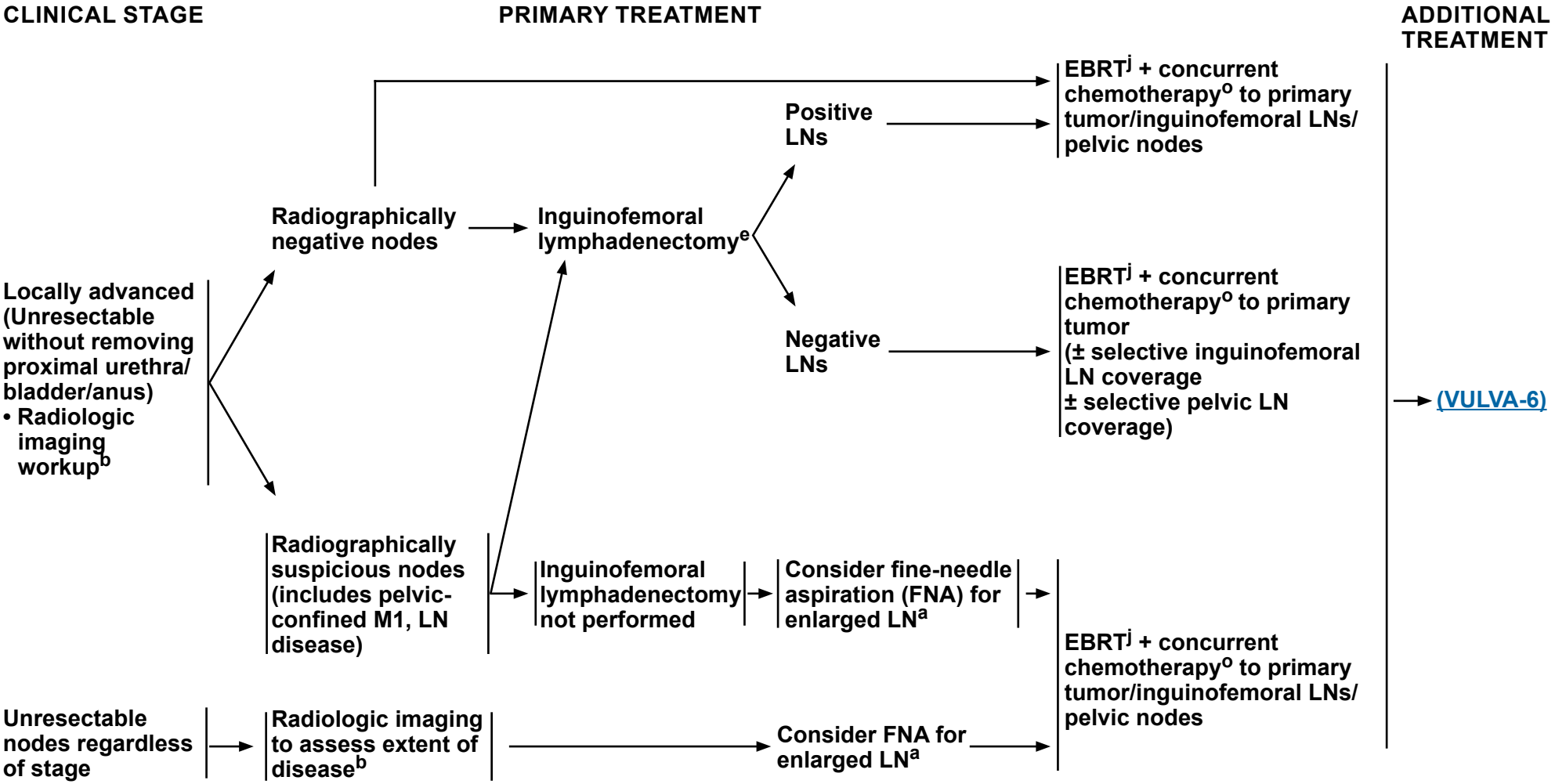
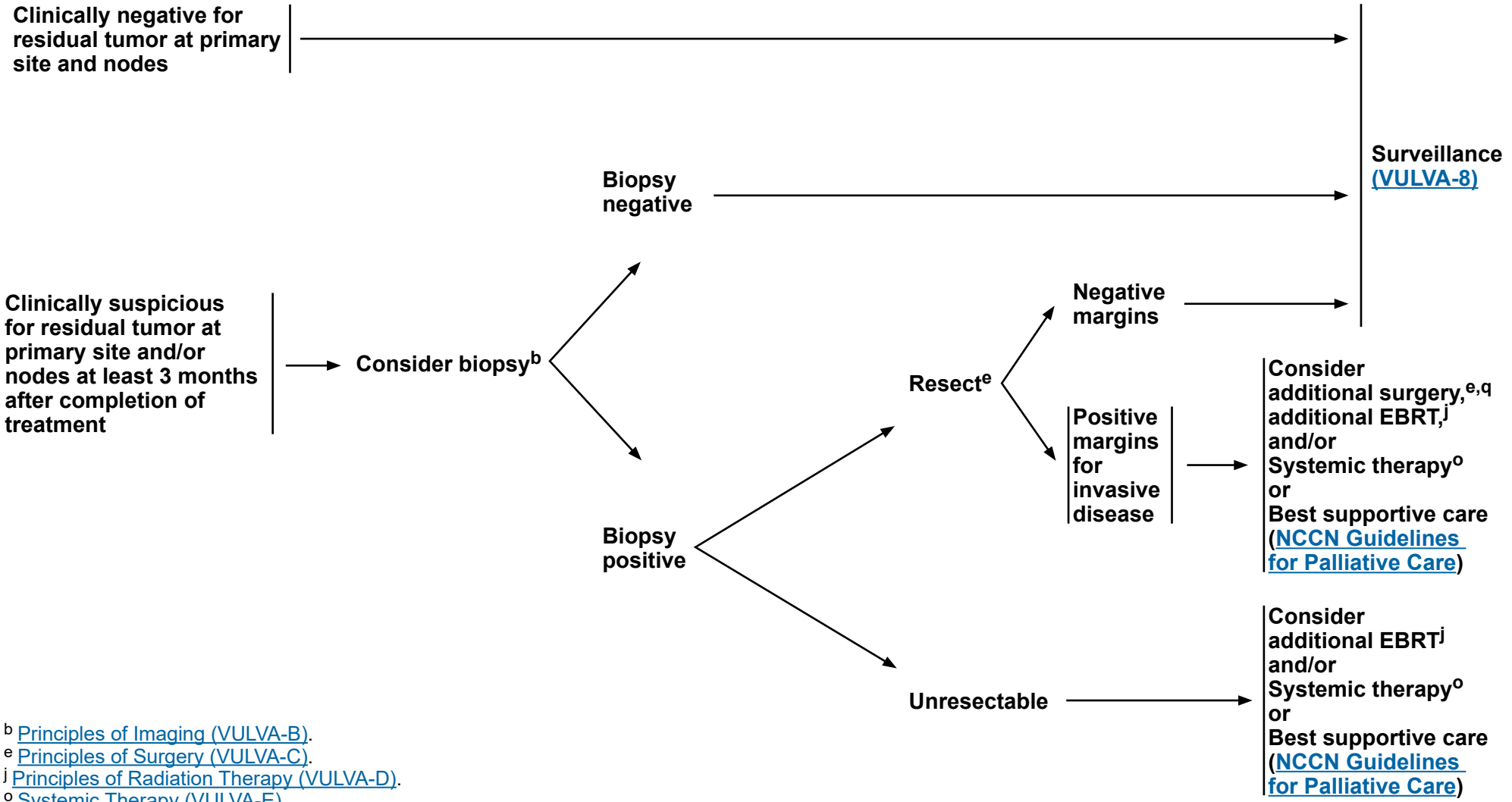


[a] Principles of Pathology (VULVA-A).
[b] Principles of Imaging (VULVA-B).
[e] Principles of Surgery (VULVA-C).
[j] Principles of Radiation Therapy (VULVA-D).
[o] Systemic Therapy (VULVA-E).

Note: All recommendations are category 2A unless otherwise indicated.

EVALUATION OF RESPONSE TO EBRT + CONCURRENT CHEMOTHERAPY

ADDITIONAL TREATMENT



[b] Principles of Imaging (VULVA-B).
[e] Principles of Surgery (VULVA-C).
[j] Principles of Radiation Therapy (VULVA-D).
[o] Systemic Therapy (VULVA-E).
[q] Consider pelvic exenteration for select cases.

Note: All recommendations are category 2A unless otherwise indicated.

CLINICAL STAGE	PRIMARY TREATMENT
Metastatic disease beyond pelvis (Stage IVB)	**EBRT[j,r] for locoregional control/symptom palliation and/or Systemic therapy[o] or Best supportive care (NCCN Guidelines for Palliative Care)**

[j] Principles of Radiation Therapy (VULVA-D).
[o] Systemic Therapy (VULVA-E).
[r] Can consider ablative therapy for 1–5 metastatic lesions if the primary has been controlled (Palma DA, et al. Lancet 2019;393:2051-2058).

Note: All recommendations are category 2A unless otherwise indicated.

SURVEILLANCE

- **Interval H&P**
  - **every 3–6 months for 2 years**
  - **every 6–12 months for 3–5 years**
  - **then annually based on patient's risk of disease recurrence**
- **Cervical/vaginal cytology screening[s,t] as indicated for the detection of lower genital tract neoplasia (may include HPV testing)**
- **Imaging as indicated based on symptoms or examination findings suspicious for recurrence[b]**
- **Laboratory assessment (CBC, blood urea nitrogen [BUN], creatinine) as indicated based on symptoms or examination findings suspicious for recurrence**
- **Clinical evaluation and management of potential long-term and late effects of treatment[u] [Also see Principles of Gynecologic Survivorship (VULVA-F), NCCN Guidelines for Survivorship, and NCCN Guidelines for Smoking Cessation]**

WORKUP

Clinically suspected recurrence

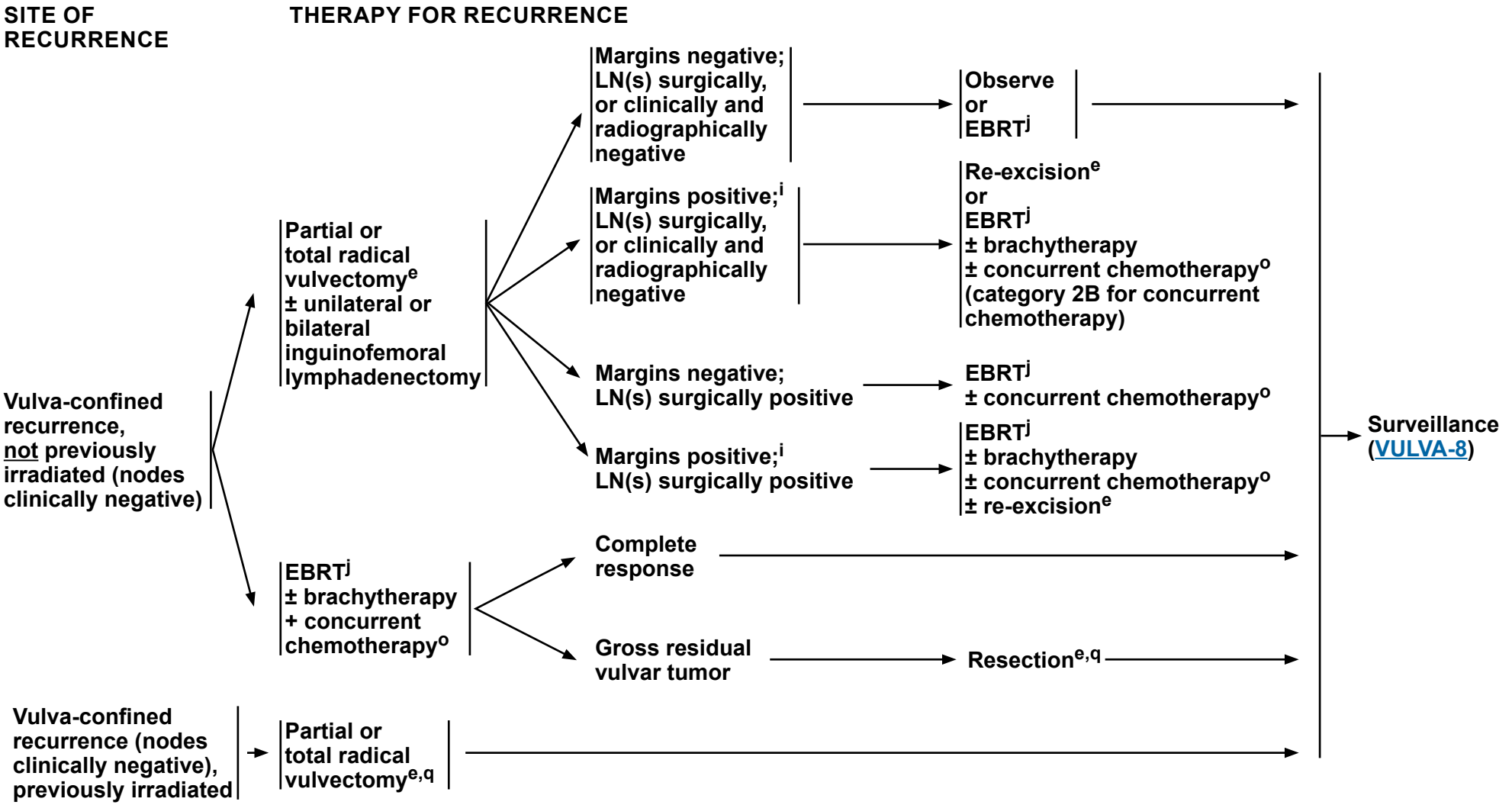
- **Imaging workup[b]**
- **Consider biopsy to confirm local and/or distant recurrence**

→ **Therapy for recurrence clinically limited to the vulva (VULVA-9)**

→ **Therapy for clinical nodal or distant recurrence (VULVA-10)**

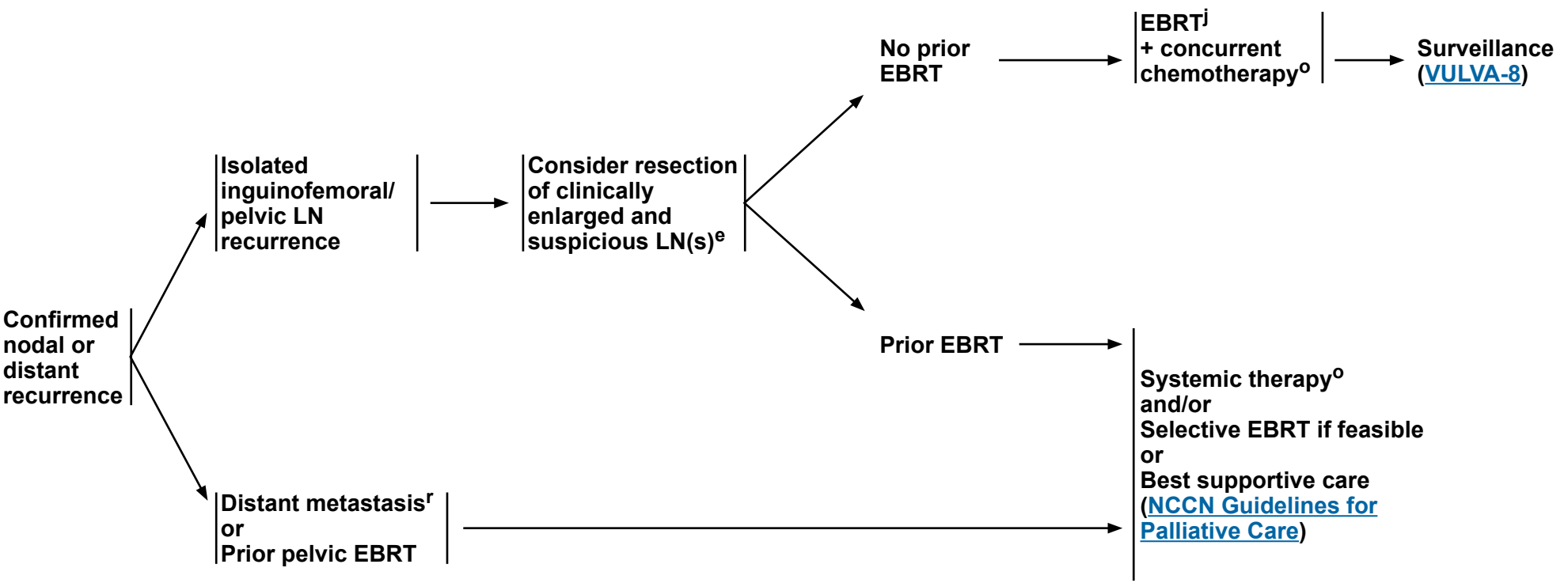
[b] Principles of Imaging (VULVA-B).
[s] Regular cytology can be considered for detection of lower genital tract dysplasia, although its value in detection of recurrent genital tract cancer is limited.
[t] The accuracy of cytology results may be affected in patients who have received pelvic radiation.
[u] Patient education should include symptoms of potential recurrence and vulvar dystrophy, periodic self-examinations, lifestyle, obesity, exercise, sexual health (including vaginal dilator use and lubricants/moisturizers, local estrogen and hormone therapy for menopause), smoking cessation, and nutrition counseling.

Note: All recommendations are category 2A unless otherwise indicated.



[e] Principles of Surgery (VULVA-C).
[i] The management of positive margins for HSIL (noninvasive disease) should be individualized.
[j] Principles of Radiation Therapy (VULVA-D).
[o] Systemic Therapy (VULVA-E).
[q] Consider pelvic exenteration for select cases.

Note: All recommendations are category 2A unless otherwise indicated.



e Principles of Surgery (VULVA-C).
j Principles of Radiation Therapy (VULVA-D).
o Systemic Therapy (VULVA-E).
r Can consider ablative therapy for 1–5 metastatic lesions if the primary has been controlled (Palma DA, et al. Lancet 2019;393:2051-2058).

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGY[1-4]

Procedure: Vulvectomy

General Principles
- Histologic grading of SCC is not well-defined and can be subjective. Two pathways of vulvar intraepithelial neoplasia (VIN) and SCC have been identified in the vulva: HPV-associated and HPV-independent.
- A meta-analysis showed that HPV-associated SCC had a better prognosis than HPV-independent SCC.

HPV-Associated
- HPV-associated SCC frequently occurs in younger patients, is frequently multifocal, is associated with classic VIN, and can be seen in association with additional sites of lower genital tract squamous neoplasia.
- Immunohistochemistry (IHC) shows strong, diffuse, block-like positive nuclear and cytoplasmic staining with p16 and wild-type p53 (heterogeneous staining pattern).

HPV-Independent
- HPV-independent VIN and SCC are identified in the setting of chronic vulvar inflammatory disorders such as lichen sclerosus.
- HPV-independent SCC is split into two main groups: those associated with *TP53* mutations and those with wild-type *TP53* status.
  - The p53 abnormal, HPV-independent SCC usually occurs in older patients, is unifocal, and is associated with differentiated VIN (dVIN).
    - IHC usually shows aberrant p53 staining (widespread, strong nuclear expression or complete absence/null expression) and patchy (negative) p16 staining.
    - The p53 abnormal SCCs have the worst clinical outcomes of the three molecular categories (HPV positive, HPV-negative/p53 mutant, and HPV-negative p53 wild-type).[5]
- Assessing the presence and depth of invasion in vulvar SCC can be challenging.
- Depth of invasion (measured in mm) has previously been from the epithelial-stromal junction of the adjacent, most superficial dermal papilla to the deepest point of invasion[6] (Figure 1, method B). Alternative ways to measure the depth of invasion have recently been proposed[7] (Figure 1, method A).

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGY[1-4]

Pathologic Assessment for Squamous Cell Carcinoma

- **Vulva**
  - **Procedure type (total or partial vulvectomy)**
  - **Depth of surgical procedure (superficial or skinning, simple, or radical)**
  - **Tumor site**
  - **Tumor size; include greatest dimension and additional two dimensions**
  - **Number of tumor foci**
  - **Histologic type**
  - **Histologic grade**
  - **Depth of invasion (in mm). Pathologists should describe their methodology for measuring depth of invasion.**
  - **Surgical resection margin status**
  - **Lymphovascular space invasion (LVSI)**
- **Other tissue/organ involvement (eg, vagina, urethra, anus, bladder mucosa, rectal mucosa, pelvic bone)**
- **LNs (when resected)[a]**
  - **SLNs should undergo ultrastaging for detection of low-volume metastasis[b]**
  - **Number of LNs with[c]:**
    - ◊ **Metastasis ≥5 mm**
    - ◊ **Metastasis ≤5 mm**
    - ◊ **Isolated tumor cells (≤0.2 mm)**
- **Additional molecular testing and biomarkers**
  - **Recommend ancillary testing to determine HPV status either by p16 IHC or RNA sequencing or HPV in situ hybridization (ISH) if available, or DNA sequencing.**
  - **Recommend p53 IHC to determine p53 status in HPV-negative tumors[8] (NGS acceptable alternative).**
  - **Consider programmed death ligand 1 (PD-L1) testing for patients with recurrent, progressive, or metastatic disease.**
  - **HER2 IHC testing (with or without reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) is recommended for advanced or recurrent/metastatic disease.**
  - **Consider comprehensive molecular profiling by an FDA-approved assay, or a validated test performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory including at least mismatch repair (MMR)/microsatellite instability (MSI), tumor mutational burden (TMB)[9], and NTRK testing for predicting rare pan-tumor targeted therapy opportunities.**

[a] In situations where SLN metastases are <2 mm, the size of greatest metastasis should be reported (VULVA-4).
[b] Ultrastaging commonly entails thin serial sectioning of the gross SLN and review of multiple hematoxylin and eosin (H&E)-stained sections with or without cytokeratin IHC for all blocks of SLNs. There is no standard protocol for LN ultrastaging.
[c] Report on the number of LNs with metastases of the following sizes: <2 mm; 2–5 mm; and >5 mm. The 2-mm threshold is used to inform treatment selection and 5-mm threshold is used to inform staging.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF PATHOLOGY

Figure 1: Depth of Invasion (Pathologists should describe their methodology for measuring depth of invasion.)

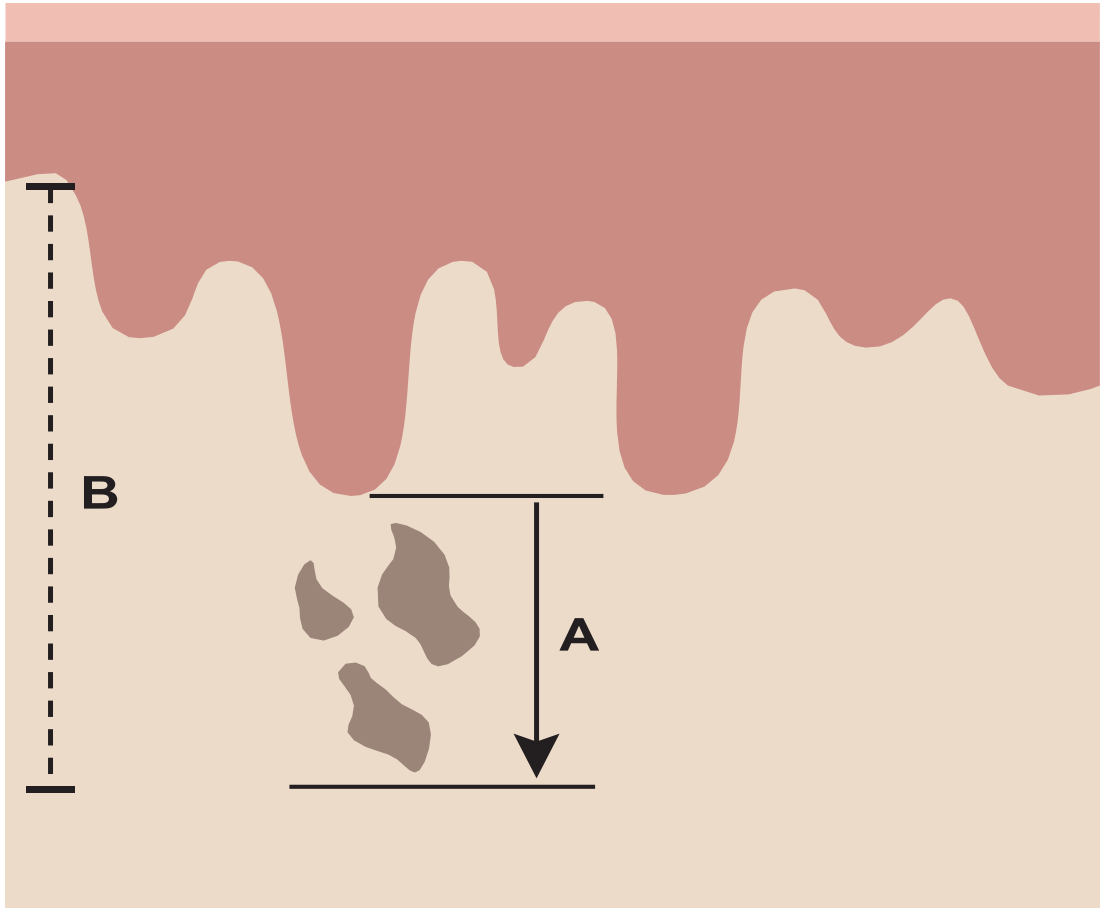


Diagram showing the new International Federation of Gynecology and Obstetrics (FIGO) (A) and previous (B) methods of measuring depth of invasion for vulvar SCC. In the new FIGO method (A), the depth of invasion is measured from the basement membrane of the deepest adjacent dysplastic/noninvasive rete ridge to the deepest point of invasion. The previous method (B) used the distance from the adjacent most superficial dermal papilla to the deepest point of invasion.

Note: All recommendations are category 2A unless otherwise indicated.

References

PRINCIPLES OF PATHOLOGY
REFERENCES

[1] Movahedi-Lankarani S, Krishnamurti U, Bell D, et al. Protocol for the Examination of Specimens from Patients with Primary Carcinoma of the Vulva. College of American Pathologists 2018.
[2] Del Pino M, Rodriguez-Carunchio L, Ordi J. Pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma. Histopathology 2013;62:161-175.
[3] Höhn AK, Brambs CE, Hiller GGR, May D, Schmoeckel E, Horn LC. 2020 WHO Classification of Female Genital Tumors. Geburtshilfe Frauenheilkd 2021;81:1145-1153.
[4] Zhang J, Zhang Y, Zhang Z. Prevalence of human papillomavirus and its prognostic value in vulvar cancer: A systematic review and meta-analysis. PLoS One 2018:13:e0204162.
[5] Kortekaas KE, Bastiaanet E, van Doorn HC, et al. Vulvar cancer subclassification by HPV and p53 status results in three clinically distinct subtypes. Gynecol Oncol 2020;159:649-656.
[6] Pecorelli S. Revised FIGO staging of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009;105:103-104.
[7] van den Einden LC, Massuger LF, Jonkman JK, et al. An alternative way to measure the depth of invasion of vulvar squamous cell carcinoma in relation to prognosis. Mod Pathol 2015;28:295-302.
[8] Tessier-Cloutier B, Kortekaas KE, Thompson E, et al. Major p53 immunohistochemical patterns in in situ and invasive squamous cell carcinomas of the vulva and correlation with TP53 mutation status. Mod Pathol 2020;33:1595-1605.
[9] Merino DM, McShane LM, Fabrizio D, et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. J Immunother Cancer 2020;8:e000147.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF IMAGING[a,1-5]

Initial Workup

- **Consider chest imaging (chest x-ray). If an abnormality is seen, then chest CT without contrast may be performed.**
- **Consider pelvis MRI to aid in surgical and/or radiation treatment planning.[b]**
  - **Consider neck/chest/abdomen/pelvis/groin fluorodeoxyglucose (FDG)-PET/CT or chest/abdomen/pelvis CT for clinical Stage II or higher tumors or if metastasis is suspected.[b]**
- **Other initial imaging should be based on symptomatology and clinical concern for metastatic disease.[b]**
- **FDG-PET/CT may be considered in patients with positive sentinel nodes to evaluate for undissected nodal disease in the groin or pelvis that needs additional treatment.**

Follow-up/Surveillance

- **CT chest/abdomen/pelvis or neck/chest/abdomen/pelvis/groin FDG-PET/CT if recurrence/metastasis is suspected.[c]**
- **Consider FDG-PET/CT and/or pelvis MRI at 3–6 months to assess treatment response after definitive primary treatment.**
- **Other imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease.[c]**

Imaging for Suspected or Documented Recurrence

- **Consider neck/chest/abdomen/pelvis/groin FDG-PET/CT if not previously performed during surveillance.**
- **Consider pelvis MRI to aid in further treatment planning.**

Footnotes

[a] MRI is performed with and without contrast and CT is performed with contrast unless contraindicated. Contrast is not required for screening chest CT.

[b] Indications may include abnormal physical exam findings; bulky vulvar tumor (≥4 cm or close to critical structures); vaginal, urethral, or anal involvement; delay in presentation or treatment; and pelvic, abdominal, or pulmonary symptoms.

[c] Indications may include abnormal physical exam findings such as palpable new mass or adenopathy, or new pelvic, abdominal, or pulmonary symptoms.

References

[1] Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. Gynecol Oncol 2017;146:3-10.

[2] Kataoka MY, Sala E, Baldwin P, et al. The accuracy of magnetic resonance imaging in staging of vulvar cancer: a retrospective multi-centre study. Gynecol Oncol 2010;117:82-87.

[3] Robertson NL, Hricak H, Sonoda Y, et al. The impact of FDG-PET/CT in the management of patients with vulvar and vaginal cancer. Gynecol Oncol 2016;140:420-424.

[4] Elit L, Reade CJ. Recommendations for follow-up care for gynecologic cancer survivors. Obstet Gynecol 2015;126:1207-1214.

[5] Viswanathan C, Kirschner K, Truong M, et al. Multimodality imaging of vulvar cancer: staging, therapeutic response, and complications. AJR AM J Roentgenol 2013; 200:1387-1400.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SURGERY: TUMOR MARGIN STATUS

- **Studies suggest a high overall incidence of local recurrence (or new primary lesions) in vulvar carcinoma.[1] Tumor margin of resection has been postulated as a significant prognostic factor for recurrence in SCC of the vulva; however, presence of dVIN and lichen sclerosus may also play a significant role in recurrence or development of new primary carcinomas.[2,3,4,5]**
- **Efforts should be made to obtain adequate gross surgical margins (at least 1 cm) at primary surgery. Recent studies have questioned the traditional (8-mm) pathologic free margin and suggested that a smaller margin may be acceptable, particularly to preserve sensitive areas on the vulva and maintain sexual function.[6,7,8]**
- **The definition of a pathologic close margin has also varied from 1–8 mm for formalin-fixed tissue.[9,10] In the setting of a close margin for invasive cancer at primary resection, observation with regular close follow-up is reasonable. Re-excision should be considered in cases with positive margin for cancer.[9,11] Adjuvant local radiation therapy (RT) is another alternative.[12] The risk-benefit ratio and morbidity of these approaches must be considered and individualized in each patient. The survival advantage of re-excision and adjuvant vulvar radiation remains to be determined.[10]**
- **Positive margins that involve the urethra, anus, or vagina may not be resectable without incurring significant potential morbidity and adverse impact on patient quality of life.**
- **Other factors including nodal status should be considered in the decision whether to perform subsequent surgery. Re-excision of close or positive vulvar tumor margins may not be beneficial in patients with metastases to the inguinal nodes that require treatment with EBRT ± chemotherapy after surgery.**

Note: All recommendations are category 2A unless otherwise indicated.

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References

PRINCIPLES OF SURGERY: SURGICAL STAGING

- Vulvar cancer is staged using the FIGO staging system (Table ST-1).[13]
- Staging involves complete surgical resection of the primary vulvar tumor(s) with at least 1-cm clinical gross margins and either a unilateral or bilateral inguinofemoral lymphadenectomy or an SLNB in select patients. Inguinofemoral lymphadenectomy removes the LNs along the inguinal ligament, within the proximal femoral triangle, and deep to the cribriform fascia.
- LN status is the most important determinant of survival.[14]
- Historically, en bloc resection of the vulvar tumor and complete bilateral inguinofemoral lymphadenectomy (resection of superficial inguinal and deep femoral nodes) were performed, but this approach was associated with significant morbidity.[15]
- The current standard involves resection of the vulvar tumor and LNs through separate incisions.[15]
- The choice of vulvar tumor resection technique depends on the size and extent of the primary lesion and may include partial or total vulvectomy, and the depth of resection may be superficial/skinning, simple, or radical.[16]
- The depth of the resection for radical vulvectomy is to the urogenital diaphragm, or median perineal fascia or periosteum of pubic bone.[17]
- There are no prospective trials comparing the resection techniques above. Retrospective data suggest there is no difference in recurrence outcome between radical partial vulvectomy compared with radical total vulvectomy.
- For a unifocal primary vulvar tumor that is <4 cm in diameter, located ≥2 cm from the vulvar midline and in the setting of clinically negative inguinofemoral LNs, a unilateral inguinofemoral lymphadenectomy or SLNB is appropriate (Principles of Surgery: Inguinofemoral Sentinel Lymph Node Biopsy [VULVA-C 4 of 6]).[18]
- For a primary vulvar tumor located within 2 cm from or crossing the vulvar midline, a bilateral inguinofemoral lymphadenectomy[18] or SLNB is recommended.
- Inguinofemoral lymphadenectomy or SLNB can be omitted in patients with stage IA primary disease with clinically negative groins due to a <1% risk of lymphatic metastases.[18]

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SURGERY: SURGICAL STAGING

- **For patients with stage IB–II disease, inguinofemoral lymphadenectomy is recommended due to a risk of >8% of lymphatic metastases.[18]**
- **A negative unilateral inguinofemoral lymphadenectomy is associated with a <3% risk of contralateral metastases.[19]**
- **Any nodes that are grossly enlarged or suspicious for metastases during the unilateral inguinofemoral lymphadenectomy should be evaluated by frozen section pathology intraoperatively in order to tailor the extent and bilaterality of the lymphadenectomy.**
- **Those with locally advanced disease may benefit from neoadjuvant radiation with concurrent platinum-based radiosensitizing chemotherapy. If a complete response is not achieved, surgical resection of the residual disease is recommended in patients with resectable disease who are appropriate surgical candidates.[18]**
- **The management of bulky inguinofemoral LNs in the setting of an unresectable or stage III–IVA primary vulvar lesion is unclear. It is reasonable to consider either: 1) primary cytoreductive surgery of the bulky LNs followed by platinum-based chemotherapy and radiation to the bilateral groins and primary vulvar tumor; or 2) platinum-based chemotherapy and radiation to the bilateral groins and primary vulvar tumor alone.[20]**

Note: All recommendations are category 2A unless otherwise indicated.

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References

PRINCIPLES OF SURGERY: INGUINOFEMORAL SENTINEL LYMPH NODE BIOPSY

- Unilateral or bilateral inguinofemoral lymphadenectomy is associated with a high rate of postoperative morbidity; 20%–40% of patients are at risk of wound complications and 30%–70% of patients are at risk for lymphedema.[21,22]
- Increasing evidence suggests that the use of SLNB of the inguinofemoral LN basin is an alternative standard-of-care approach to lymphadenectomy in select patients with SCC of the vulva.[23,24]
- SLNB results in decreased postoperative morbidity without compromising detection of LN metastases.[23,25]
- Prospective, cooperative group trials have evaluated the SLN technique and demonstrate feasibility, safety, validity, and a low risk of groin recurrences with this surgical approach in vulvar cancer.[23,24]
- Candidates for SLNB include patients with negative clinical groin examination and/or imaging, and a primary unifocal vulvar tumor size of <4 cm.[24,26,27]
- If SLNB is considered, it should be performed by an experienced high-volume SLN surgeon, as high-volume surgeons exhibit improved SLN detection rates.[24,26]
- Increased sensitivity of SLN detection is observed when both radiocolloid and blue dye are used.[23,24,25] The radiocolloid most commonly injected into the vulvar tumors is technetium-99m sulfur colloid. It is most commonly injected 2–4 hours prior to the vulvectomy and lymphadenectomy procedure. A preoperative lymphoscintigraphy may be performed to aid in anatomically locating the sentinel node. The blue dye most commonly used is Isosulfan Blue 1%. Approximately 4 cc of dye is injected peritumorally using a four-point injection technique at 2, 5, 7, and 10 o'clock. The blue dye is injected in 4 quadrants intradermally around the leading edges of the tumor.
- It is recommended that the SLN procedure is performed prior to the excision of the vulvar tumor, so as not to disrupt the lymphatic network between the primary vulvar tumor and the inguinofemoral LN basin. Additionally, the injected blue dye will only transiently localize (ie, for 30–60 minutes) in the first group of nodes that correspond to the primary vulvar tumors. Indocyanine green (ICG) with technetium has also been used for SLN mapping in vulvar cancer with encouraging results.
- Use of a gamma probe to detect the injected radiocolloid within the inguinofemoral region is recommended prior to making the groin incision in order to tailor the location and size of the incision.
- A side-specific complete inguinofemoral lymphadenectomy is recommended if an ipsilateral SLN is not detected.
- Completion inguinofemoral lymphadenectomy is the preferred approach in the presence of metastases >2 mm in diameter in the SLNs.[28]
- For lateralized and near-midline tumors with unilateral SLN metastasis, unilateral groin treatment by either inguinofemoral lymphadenectomy or RT is acceptable.
- For midline tumors with unilateral SLN metastasis, unilateral groin treatment can be performed if the contralateral groin has negative sentinel node or negative inguinofemoral lymphadenectomy.[29,30]
- Selective frozen section of sentinel node may guide the intraoperative decision regarding need for completion unilateral or bilateral inguinofemoral lymphadenectomy.

Note: All recommendations are category 2A unless otherwise indicated.

References

PRINCIPLES OF SURGERY: SLNB MANAGEMENT

Table 1: Management of Sentinel Lymph Node(s) Mapping

Lesion Location	Sentinel Lymph Node Mapping	Management
Midline	None	Bilateral inguinofemoral lymphadenectomy
	Unilateral	Sentinel lymph node biopsy (SLNB) on mapped side + inguinofemoral lymphadenectomy on non-mapped side
	Bilateral	Bilateral SLNB
Lateral ambiguous/Near midline	None	Bilateral inguinofemoral lymphadenectomy
	Ipsilateral	Ipsilateral SLNB[b]
	Bilateral	Bilateral SLNB
	Contralateral	Ipsilateral inguinofemoral lymphadenectomy + contralateral SLNB
Lateral[a]	None	Ipsilateral inguinofemoral lymphadenectomy
	Ipsilateral	Ipsilateral SLNB
	Bilateral	Bilateral SLNB
	Contralateral	Ipsilateral inguinofemoral lymphadenectomy + contralateral SLNB

Lesion locations:
- **Midline: Crossing or involving the midline**
- **Lateral ambiguous/Near midline: Located within 2 cm of the midline, but not crossing or involving the midline**
- **Lateral: Greater than 2 cm from the midline**

[a] True lateral lesions are rare as 2 cm often extends lateral to the genitocrural fold.
[b] Given limited data regarding management of lesions that do not involve the midline but are not true lateral lesions (lateral ambiguous/near midline), it is reasonable to consider only ipsilateral LN evaluation in patients who have preoperative lymphoscintigraphy that demonstrates ipsilateral drainage only. A contralateral LN evaluation should be performed in patients who do not undergo preoperative lymphoscintigraphy, and in patients where preoperative lymphoscintigram demonstrates contralateral drainage.[30]

Note: All recommendations are category 2A unless otherwise indicated.

References

PRINCIPLES OF SURGERY
REFERENCES

[1] Rouzier R, Haddad B, Plantier F, et al. Local relapse in patients treated for squamous cell vulvar carcinoma: incidence and prognostic value. Obstet Gynecol 2002;100:1159-1167.
[2] Te Grootenhuis NC, Pouwer AW, de Bock GH, et al. Margin status revisited in vulvar squamous cell carcinoma. Gynecol Oncol 2019;154:266-275.
[3] Pleunis N, Leermakers MEJ, van der Wurff AA, et al. Surgical margins in squamous cell carcinoma, different for the vulva? Eur J Surg Oncol 2018;44:1555-1561.
[4] Heaps JM, Fu YS, Montz FJ, et al. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol 1990;38:309-314.
[5] De Hullu JA, Hollema H, Lolkema S, et al. Vulvar carcinoma. The price of less radical surgery. Cancer 2002;95:2331-2338.
[6] Woelber L, Griebel L, Eulenburg C, et al. Role of tumour-free margin distance for loco-regional control in vulvar cancer--a subset analysis of the Arbeitsgemeinschaft Gynakologische Onkologie CaRE-1 multicenter study. Eur J Cancer 2016;69:180-188.
[7] Woelber L, Choschzick M, Eulenburg C, et al. Prognostic value of pathological resection margin distance in squamous cell cancer of the vulva. Ann Surg Oncol 2011;18:3811-3818.
[8] Groenen SMA, Timmers PJ, Burger CW. Recurrence rate in vulvar carcinoma in relation to pathological margin distance. Int J Gynecol Cancer 2010;20:869-873.
[9] Ioffe YJ, Erickson BK, Foster KE, et al. Low yield of residual vulvar carcinoma and dysplasia upon re-excision for close or positive margins. Gynecol Oncol 2013;129:528-532.
[10] Bedell SM, Hedberg C, Griffin A, et al. Role of adjuvant radiation or re-excision for early stage vulvar squamous cell carcinoma with positive or close surgical margins. Gynecol Oncol 2019;154:276-279.
[11] Arvas M, Kahramanoglu I, Bese T, et al. The role of pathological margin distance and prognostic factors after primary surgery in squamous cell carcinoma of the vulva. Int J Gynecol Cancer 2018;28:623-631.
[12] Faul CM, Mirmow D, Huang Q, et al. Adjuvant radiation for vulvar carcinoma: improved local control. Ing J Radiat Oncol Biol Phys 1997;38:381-389.
[13] Olawaiye AB, Cotler J, Cuello MA, et al. FIGO staging for carcinoma of the vulva: 2021 revision. Int J Gynecol Obstet 2021;155:43-47.
[14] Burger MP, Hollema H, Emanuels AG, et al. The importance of the groin node status to survival of T1 and T2 vulvar carcinoma patients. Gynecol Oncol 1995;57:327-334.
[15] DiSaia PJ, Creasman WT, Rich WM. An alternate approach to early cancer of the vulva. Am J Obstet Gynecol 1979;133:825-832.
[16] Micheletti L, Haefner H, Zalewski K, et al. The International Society for the study of vulvovaginal disease surgical oncological procedure definitions committee "surgical terminology for vulvar treatment". J Low Genit Tract Dis 2020;24:62-68.
[17] De Hullu JA, Hollema H, Lolkema S, et al. Vulvar carcinoma. The price of less radical surgery. Cancer 2002;95:2331-2338.
[18] Stehman FB, Look KY. Carcinoma of the vulva. Obstet Gynecol 2006;107:719-733.
[19] Gonzalez-Bosquet J, Magrina JF, Magtibay PM, et al. Patterns of inguinal groin node metastases in squamous cell carcinoma of the vulva. Gynecol Oncol 2007;105:742-746.
[20] Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. Gynecol Oncol 2012;124:529-533.
[21] DiSaia PJ, Creasman WT, Rich WM. An alternate approach to early cancer of the vulva. Am J Obstet Gynecol 1979;133:825-832.
[22] Carlson JW, Kauderer J, Hutson A, et al. GOG 244, the lymphedema and gynecologic cancer (LEG) study: Incidence and risk factors in newly diagnosed patients. Gynecol Oncol 2020;156:467-474.
[23] Van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel lymph node dissection is safe in the treatment of early-stage vulvar carcinoma. J Clin Oncol 2008;26:884-889.
[24] Levenback CF, Ali S, Coleman RL, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. J Clin Oncol 2012;30:3786-3791.
[25] Oonk MH, van Hemel BM, Hollema H, et al. 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. Lancet Oncol 2010;11:646-652.
[26] Covens A, Vella ET, Kennedy EB, et al. Sentinel lymph node biopsy in vulvar cancer: Systematic review, meta-analysis and guideline recommendations. Gynecol Oncol 2015;137:351-361.
[27] Te Grootenhuis NC, van der Zee AG, van Doorn HC, et al. Sentinel nodes in vulvar cancer: Long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I. Gynecol Oncol 2016;140:8-14.
[28] Oonk MHM, Slomovitz B, Baldwin PJW, et al. Radiotherapy versus inguinofemoral lymphadenectomy as treatment for vulvar cancer patients with micrometastases in the sentinel node: Results of GROINSS-V II. J Clin Oncol 2021;39:3623-3632.
[29] Van der Kolk WL, Van der Zee AGJ, Slomovitz BM, et al. Unilateral inguinofemoral lymphadenectomy in patients with early-stage vulvar squamous cell carcinoma and a unilateral metastatic sentinel lymph node is safe. Gynecol Oncol 2022;167:3-10.
[30] Coleman RL, Ali S, Levenback CF, et al. Is bilateral lymphadenectomy for midline squamous carcinoma of the vulva always necessary? An analysis from Gynecologic Oncology Group (GOG) 173. Gynecol Oncol 2013;128:155-159.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

General Principles

- **RT is often used in the treatment of patients with vulvar cancer as adjuvant therapy following initial surgery, as part of primary therapy in locally advanced disease, or for secondary therapy/palliation in recurrent/metastatic disease.**
- **Radiation technique and doses are important to maximize tumor control while limiting adjacent normal tissue toxicity.**
- **Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement. In general, tumor-directed EBRT is directed to the vulva and/or inguinofemoral, external, and internal iliac nodal regions. Brachytherapy can sometimes be used as a boost to anatomically amenable primary tumors. Careful attention should be taken to ensure adequate tumor coverage by combining clinical examination, imaging findings, and appropriate nodal volumes at risk to define the target volume. For example, invasion into the anus above the pectinate line would necessitate coverage of the perirectal nodes.[1,2]**
- **Ensure coverage of gross tumor burden with margin. In highly selected cases where only a superficial vulvar target is to be treated, an enface electron beam may be used.**
- **Utilization of imaging studies are an important part of the treatment planning process. The use of CT-based treatment planning and conformal blocking is considered the standard of care for EBRT.**
- **Historically, a widely disparate range of approaches has been described. In an attempt to better standardize RT use and techniques, a recent international survey, with consequent recommendations, has been reported.[3]**
- **Acute effects during RT (eg, diarrhea, bladder irritation, fatigue, mucocutaneous reaction) are expected to some degree in most patients, and can be further accentuated by concurrent chemotherapy. These toxicities should be aggressively managed (eg, local skin care, symptomatic medications), and treatment breaks should be avoided or minimized. Many patients may develop an overgrowth of *Candida albicans*; treatment with oral and local antifungal agents will markedly reduce skin reaction. If a bacterial infection develops, prompt recognition and appropriate treatment is essential. These acute effects generally resolve several weeks after completion of radiation.**
- **Postoperative adjuvant treatment should be initiated as soon as adequate healing is achieved, preferably within 6–8 weeks.**

Note: All recommendations are category 2A unless otherwise indicated.

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References

PRINCIPLES OF RADIATION THERAPY

Treatment Information

- **Target Volumes**
  - **The target is best defined by both physical examination and CT-based treatment planning; contouring of the target structures is recommended. Radio-opaque markers should be placed on key landmarks at the time of simulation to assist in definition of the primary target volume.**
  - **MRI and/or PET imaging may be fused with the planning CT to aid in the delineation of gross disease. Consensus guidelines for clinical target volume (CTV) definition have been developed and are recommended when developing a treatment plan.[3]**
  - **Intensity-modulated RT (IMRT) is recommended for better dose delivery to target and sparing of target, with 2D/3D technique reserved for urgent/emergent treatment starts with prompt transition to IMRT in definitive cases, or for palliative treatment.**
- **Indications**
  - **Postoperative indications for treating the primary site include close/positive margin, LVSI, and >5-mm depth of invasion. Additionally, groin involvement may be considered a relative indication to include the primary site. Use of a midline block (to avoid toxicity to sensitive central structures) in stage III–IV vulvar cancer has been associated with a high rate of central recurrence and is usually discouraged. Conversely, there may be clinical situations in which it is desirable to cover the primary site only and avoid the nodes.**
  - **In both the locally advanced and postoperative settings, especially when there are ≥2 LNs pathologically positive, the bilateral inguinal and pelvic lymphatic regions are typically included in the radiotherapy CTV.**
  - **If there are clinically or radiographically suspicious LNs (≥1), then bilateral pelvic and groin radiotherapy is recommended.**
  - **If the groin is clinically node negative, but pathologically node positive (by sentinel node procedure or dissection), then the number of positive nodes, size of LN metastasis, features of the primary lesion, and extent of surgery may impact recommendations for adjuvant RT.[4]**
    - **If there is a single positive SLN and no completion inguinofemoral lymphadenectomy done, then adjuvant RT or chemoradiation is recommended regardless of size of LN metastasis. If the single positive node is ≥2 mm, adjuvant RT alone to 50 Gy is inferior to inguinofemoral lymphadenectomy. Therefore, in these cases, consider adding chemotherapy or increasing radiation dose to 54–60 Gy or both.**
    - **If there are ≥2 pathologic positive nodes or extracapsular extension (ECE) is present, then adjuvant RT or chemoradiation is recommended.**
    - **In the setting of a single pathologic LN without ECE and a completion inguinofemoral lymphadenectomy (IFLD), there are scenarios where adjuvant RT or chemoradiation may be favored such as larger primary tumor size, larger LN size, inadequate LN dissection, LN ratio >20%, presence of LVSI, or radiographically suspicious findings. We favor evaluation of these patients by a radiation oncologist and consideration of postoperative PET imaging to help with decision-making.**
    - **There are some data that suggest the contralateral groin could be observed in patients with documented ipsilateral drainage, a lateralized lesion, and small primary tumor.**

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

Treatment Information – Intensity-Modulated Radiation Therapy (IMRT)[5]

- The vulvar and nodal targets should be contoured on the planning CT. Any gross vulvar disease should be contoured as a gross tumor volume (GTV) and include any visible and/or palpable extension. The vulvar CTV target is defined as the GTV or tumor bed plus the adjacent skin, mucosa, and subcutaneous tissue of the vulva excluding bony tissue. A wire placed clinically to define the vulvar skin borders and the GTV during CT simulation is essential. In addition, a marker on the anus, urethra, clitoris, and the wiring of any scars will aid in planning.
- To ensure adequate distal margin on the vulvar target volume, a "false structure" or bolus should be placed over the vulva for treatment planning purposes. Doses to the target areas should be confirmed using thermoluminescent dosimeter (TLD) at first treatment.
- Symmetrical geometric expansions on the vessels should NOT be used for the inguinofemoral nodes. The inguinofemoral nodal CTV will extend laterally from the inguinofemoral vessels to the medial border of the sartorius and rectus femoris muscles, posteriorly to the anterior vastus medialis muscle, and medially to the pectineus muscle or 2.5–3 cm medially from the vessels. Anteriorly, the volume should extend to the anterior border of the sartorius muscle (the most anterior muscle on the lateral inguinofemoral border). The caudal extent of the inguinofemoral nodal basin is the top of the lesser trochanter of the femur.[2]
- The pelvic nodal CTV is the vasculature of the bilateral external iliac, obturator, and internal iliac nodal regions with a minimum of 7 mm of symmetrical expansion excluding bone and muscle.
- The groin CTV volume will not extend outside the skin and should be trimmed by 3 mm in the absence of skin involvement (with skin involvement, the CTV should extend to the skin with bolus material applied during treatment). Planning target volume (PTV) expansion is then 7–10 mm.
- Image-guided IMRT is an essential component of treatment (to account for vulva edema or marked tumor regression).
- Planning should be taken with care to respect normal tissue tolerances such as rectum, bladder, small bowel, and femoral head and neck.[6]

General Treatment Information

- Bolus should be used to ensure adequate dosing to superficial target volume both at the primary site and when LNs are just below the skin surface.
- TLD, optically stimulated luminescence dosimeter (OSLD), or electronic dosimetry to skin may be used for dose verification.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF RADIATION THERAPY

Dosing Prescription Regimen

- **The target tissues should be treated once daily, 5 days per week. Breaks from treatment should be minimized. Adequate dosing is crucial and can be accomplished with either 3D conformal RT (3D-CRT) approaches or IMRT as long as care is given to assure adequate dosing and coverage of tissues at risk for tumor involvement.[1,7] IMRT is preferred over 3D-CRT to reduce dose to normal tissues and to allow for dose escalation.**
- **Doses range from 45–50.4 Gy in 25–28 fractions (1.8 Gy fractions) for adjuvant therapy to 59.4–64.8 Gy in 33–36 total fractions (1.8 Gy fractions) for unresectable disease. In select cases, bulky/persistent primary disease or large nodes that are unresectable may be boosted to 70 Gy.**
- **High recurrence rates have been noted with 50 Gy alone for >2 mm of nodal involvement, or ECE; dose escalation to 54–60 Gy and/or concurrent systemic therapy, preferably on the GROINS-V III protocol, can be considered.8**
- **Suggested dosing to areas of risk:**
  - **Gross primary vulva disease = 60–70 Gy**
  - **Primary surgical bed (postoperative, negative margins) = 45–50 Gy**
  - **Primary surgical bed (postoperative close or positive margins) = 54–60 Gy**
  - **Clinically and/or radiographically uninvolved inguinofemoral LNs = 45–50 Gy**
  - **Inguinofemoral LNs (positive, no ECE or gross residual disease) = 50–55 Gy**
  - **Inguinofemoral LNs (ECE) = 54–64 Gy**
  - **LNs (gross residual or unresectable disease) = 60–70 Gy**

Note: All recommendations are category 2A unless otherwise indicated.

References

PRINCIPLES OF RADIATION THERAPY
REFERENCES

[1] Beriwal S, Shukla G, Shinde A, et al. Preoperative intensity modulated radiation therapy and chemotherapy for locally advanced vulvar carcinoma: analysis of pattern of relapse. Int J Radiat Oncol Biol Phys 2013;85:1269-1274.
[2] Kim CH, Olson AC, Kim H, Beriwal S. Contouring inguinal and femoral nodes; how much margin is needed around the vessels? Pract Radiat Oncol 2012;2:274-278.
[3] Gaffney DK, King B, Viswanathan AN, et al. Consensus recommendations for radiation therapy contouring and treatment of vulvar carcinoma. Int J Radiat Oncol Biol Phys 2016;95:1191-1200.
[4] Cao Y, Viswanathan A. When is it safe to omit contralateral groin management in unilateral sentinel node-positive early stage vulvar cancer? Gynecol Oncol 2022;167:1-2.
[5] Rishi A, Rollins M, Ahmed KA, et al. High-dose intensity-modulated chemoradiotherapy in vulvar squamous cell carcinoma: Outcome and toxicity. Gynecol Oncol 2020;156:349-356.
[6] Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86:27-33.
[7] Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. Gynecol Oncol 2012;124:529-533.
[8] Gien LT, Slomovitz B, Van der Zee A, Oonk M. Phase II activity trial of high-dose radiation and chemosensitization in patients with macrometastatic lymph node spread after sentinel node biopsy in vulvar cancer: GROningen INternational Study on Sentinel nodes in Vulvar cancer III (GROINSS-V III/NRG-GY024). Int J Gynecol Cancer 2023;33:619-622.

Note: All recommendations are category 2A unless otherwise indicated.

SYSTEMIC THERAPY[a,b,1] (REGIMENS ARE EXTRAPOLATED FROM CERVICAL CANCER)

Chemoradiation	Advanced or Recurrent/Metastatic Disease	
	First-Line Therapy[c]	Second-Line or Subsequent Therapy[c]
Preferred Regimens • Cisplatin • Carboplatin if cisplatin intolerant **Other Recommended Regimens** • Cisplatin/gemcitabine[2] • Cisplatin/fluorouracil • If single-agent cisplatin or carboplatin are unavailable: ▸ Capecitabine/mitomycin[3] ▸ Gemcitabine[4] ▸ Paclitaxel[5,6]	**Preferred Regimens** • Cisplatin/paclitaxel/bevacizumab[d] • Cisplatin/paclitaxel • Carboplatin/paclitaxel • Pembrolizumab + cisplatin/paclitaxel ± bevacizumab[d,e] • Pembrolizumab + carboplatin/paclitaxel ± bevacizumab[d,e] • Carboplatin/paclitaxel/bevacizumab[d] **Other Recommended Regimens** • Cisplatin • Carboplatin	**Other Recommended Regimens** • Paclitaxel • Cemiplimab[e,7,8] • Erlotinib (category 2B)[9] • Cisplatin/gemcitabine (category 2B) **Useful in Certain Circumstances (Biomarker-directed therapy)** • TMB-high (TMB-H) ▸ Pembrolizumab[e,f,10] • PD-L1–positive ▸ Pembrolizumab[e,g] • MSI-high (MSI-H)/MMR deficient (dMMR) tumors[11] ▸ Pembrolizumab[e,11] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[12] • HPV-related tumor ▸ Nivolumab[e,h,13] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib ▸ Repotrectinib[i,14]

[a] Cisplatin, carboplatin, and paclitaxel may cause drug reactions (see NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-D]).
[b] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[c] If not used previously, first-line agents can be used as second-line or subsequent therapy as clinically appropriate.
[d] Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.
[e] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f] For the treatment of patients with unresectable or metastatic TMB-H [≥10 mutations/megabase (mut/Mb)] tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.
[g] Recommended for disease progression on or after chemotherapy in patients whose tumors express PD-L1 (combined positive score [CPS] ≥1)
[h] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[i] *NTRK*-positive tumors that are naive to prior *NTRK*-targeted therapy or have progressed on prior *NTRK* therapy.

Note: All recommendations are category 2A unless otherwise indicated.

References

SYSTEMIC THERAPY
REFERENCES

[1] Reade CJ, Eiriksson LR, Mackay H. Systemic chemotherapy in squamous cell carcinoma of the vulva: current status and future directions. Gynecol Oncol 2014;132:780-789.
[2] Horowitz NS, Deng W, Peterson I, et al. Phase II trial of cisplatin, gemcitabine, and intensity-modulated radiation therapy for locally advanced vulvar squamous cell carcinoma: NRG Oncology/GOG Study 279. J Clin Oncol 2024:42;1914-1921.
[3] Lorvidhaya V, Chitapanaarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. Int J Radiat Oncol Biol Phys 2003;55:1226-1232.
[4] Pattaranutaporn P, Thirapakawong C, Chansilpa Y, et al. Phase II study of concurrent gemcitabine and radiotherapy in locally advanced stage IIIB cervical carcinoma. Gynecol Oncol 2001;81:404-407.
[5] Candelaria M, Garcia-Arias A, Cetina L, et al. Radiosensitizers in cervical cancer. Cisplatin and beyond. Radiat Oncol 2006;1:15.
[6] Cerrotta A, Gardan G, Raspagliesi F, et al. Concurrent radiotherapy and weekly paclitaxel for locally advanced or recurrent squamous cell carcinoma of the uterine cervix. A pilot study with intensification of dose. Eur J Gynaecol Oncol 2002;23:115-119.
[7] Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med 2018;379:341-351.
[8] Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med 2022;386:544-555.
[9] Horowitz NS, Olawaiye AB, Borger DR, et al. Phase II trial of erlotinib in women with squamous cell carcinoma of the vulva. Gynecol Oncol 2012;127:141-146.
[10] Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353-1365.
[11] Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1-10.
[12] Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: Primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol 2024;42:47-58.
[13] Naumann RW, Hollebecque A, Meyer T, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: Results from the phase I/II CheckMate 358 trial. J Clin Oncol 2019;37:2825-2834.
[14] Solomon B, Drilon A, Lin JJ, et al. Repotrectinib in patients with NTRK fusion-positive advanced solid tumors, including non-small cell lung cancer: update from the phase 1/2 TRIDENT-1 trial. Poster presented at the European Society for Medical Oncology Congress;October 20–24, 2023; Madrid, Spain.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF GYNECOLOGIC SURVIVORSHIP

Physical Effects

- Gynecologic cancer treatment typically involves surgery, chemotherapy, hormone therapy, RT, and/or immunotherapy. These treatments cause acute, short-term, and long-term toxicities.
- Surgical approaches may be extensive and pose risks such as adhesion formation, which may cause pain and may contribute to small bowel obstruction, urinary or gastrointestinal complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a variety of urinary, bowel, and/or sexual effects), and lymphedema.
- Chemotherapy agents vary, although commonly used regimens may pose a significant risk of neurotoxicity, cardiac toxicity, development of hematologic cancers, and cognitive dysfunction.
- Long-term estrogen deprivation may cause symptoms such as hot flashes, vaginal dryness, and bone loss.
- RT may cause long-term complications (eg, fibrosis, vulvovaginal atrophy) and may predispose patients to secondary cancers of the subcutaneous tissue, and/or underlying organs that are proximal to the radiation field.
- Prior pelvic RT may contribute to bone loss and increase the risk of pelvic fractures. Consider bone density testing and prophylactic use of bisphosphonates, particularly in patients with osteoporosis.
- Immunotherapy use is emerging, and to date, long-term effects of these treatments are unknown.

Psychosocial Effects

- Psychosocial effects after cancer may be psychological (eg, depression, anxiety, fear of recurrence, altered body image), financial (eg, return to work, insurance concerns), and/or interpersonal (eg, relationships, sexuality, intimacy) in nature.

Clinical Approach

- All gynecologic cancer survivors should receive regular general medical care that focuses on managing chronic disease, monitoring cardiovascular risk factors, providing recommended vaccinations, and encouraging adoption of a healthy lifestyle.
- In order to assess the late and long-term effects of gynecologic cancers, clinicians should comprehensively document the patient's history, conduct a thorough physical examination, and provide any necessary imaging and/or laboratory testing. All patients, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness. Referral to appropriate specialty providers (eg, physical therapy, pelvic floor therapy, sexual therapy, psychotherapy) is recommended. As most treatments for gynecologic cancers will cause sexual dysfunction, early menopause, and infertility, special attention to the resultant medical and psychosocial implications is needed.
- Post-radiation use of vaginal dilators and moisturizers is recommended.
- For treatment-related menopause, hormone therapy should be considered.
- Communication and coordination with all clinicians involved in the care of survivors, including primary care clinicians, is critical. Providing cancer survivors with a summary of their treatment and recommendations for follow-up is recommended.

Additional Guidance

- NCCN Guidelines for Distress Management
- NCCN Guidelines for Smoking Cessation
- NCCN Guidelines for Survivorship

Note: All recommendations are category 2A unless otherwise indicated.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Vulvar and Vulvovaginal Melanoma

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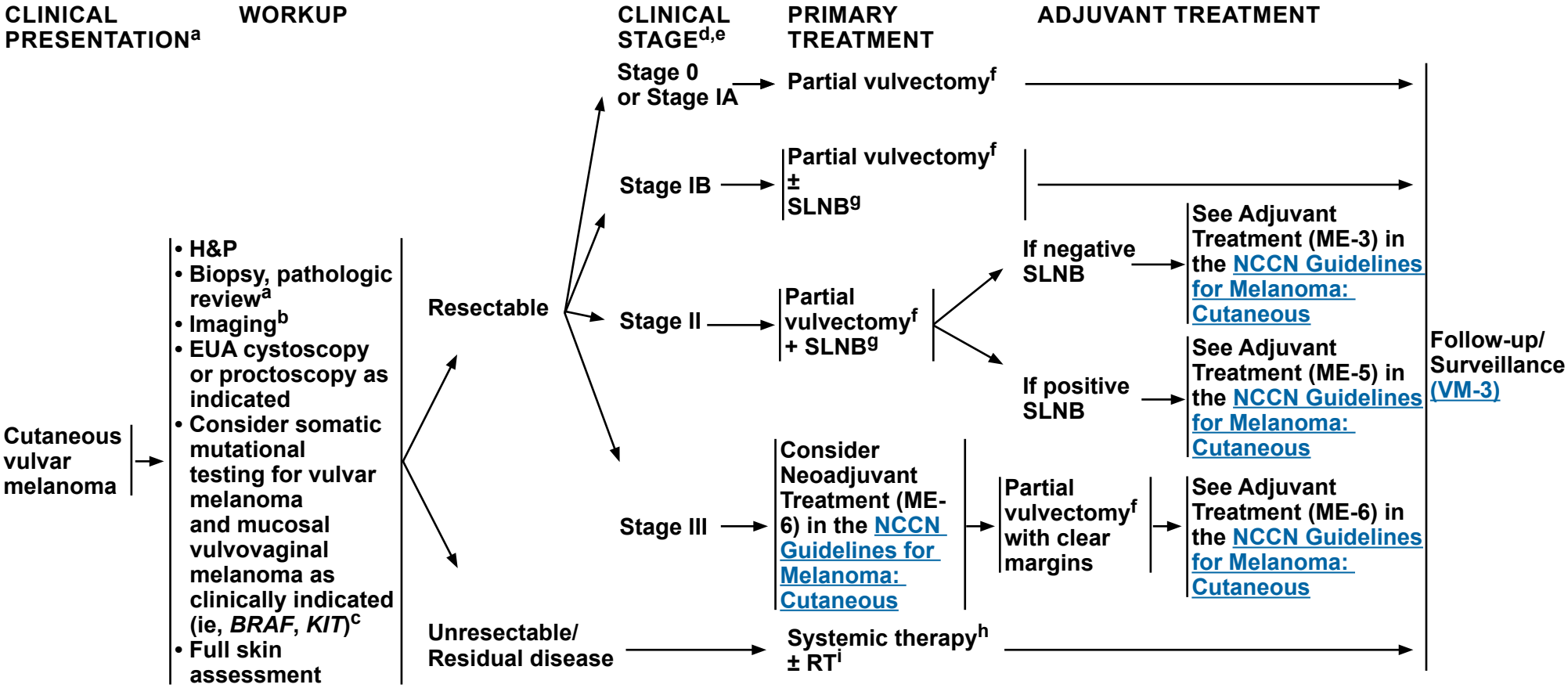

[a] Clinical presentation: Cutaneous vulvar melanoma is defined as lesions that occur on the vulva vestibule outside Hart's line; mucosal vulvovaginal melanoma is defined as lesions that occur on the vulva vestibule inside Hart's line.
[b] See Principles of Imaging (ME-D) in the NCCN Guidelines for Melanoma: Cutaneous.
[c] See Principles of Molecular Testing (ME-C) in the NCCN Guidelines for Melanoma: Cutaneous.
[d] Vulvovaginal melanoma should be staged the same as cutaneous melanoma. Clinical staging for cutaneous vulvar melanoma and vulvovaginal melanoma should be done using the AJCC staging system (TNM staging system). See Staging (ST-1) in the NCCN Guidelines for Melanoma: Cutaneous.
[e] See Principles of Biopsy and Pathology (ME-B) in the NCCN Guidelines for Melanoma: Cutaneous.
[f] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-E) in the NCCN Guidelines for Melanoma: Cutaneous. Based on limited data, topical imiquimod may be helpful in selected cases of vulvar melanoma in situ (MIS) when histologic clearance is not possible surgically.
[g] See Principles of Sentinel Lymph Node Biopsy (SLNB) (ME-F) in the NCCN Guidelines for Melanoma: Cutaneous.
[h] See Systemic Therapy for Metastatic or Unresectable Disease (MELSYS-1) in the NCCN Guidelines for Melanoma: Cutaneous.
[i] Principles of Radiation Therapy (VM-A).

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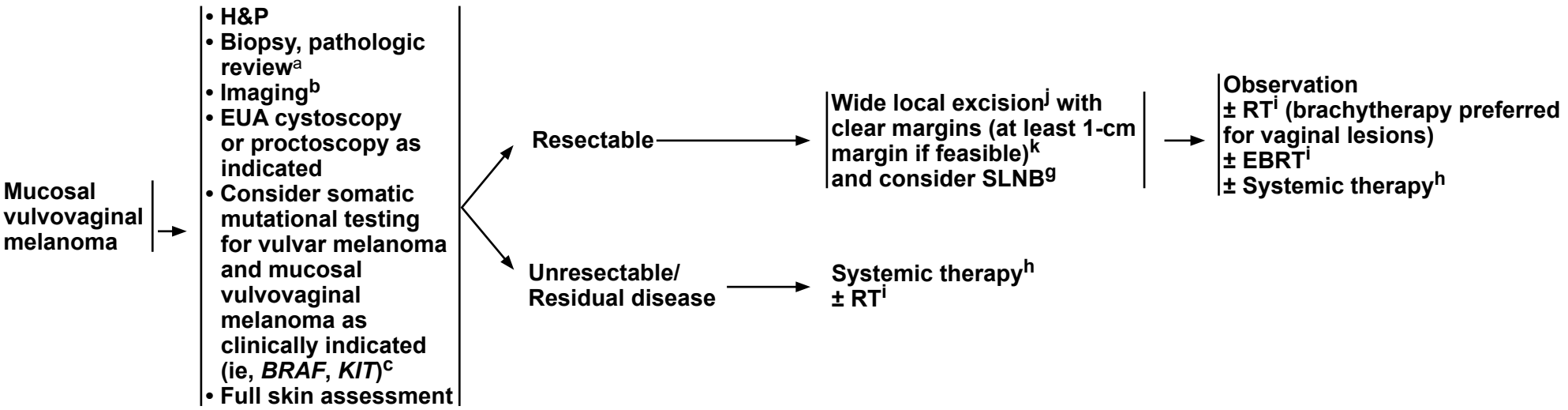

[a] Clinical presentation: Cutaneous vulvar melanoma is defined as lesions that occur on the vulva vestibule outside Hart's line; mucosal vulvovaginal melanoma is defined as lesions that occur on the vulva vestibule inside Hart's line.
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[e] See Principles of Biopsy and Pathology (ME-B) in the NCCN Guidelines for Melanoma: Cutaneous.
[g] See Principles of Sentinel Lymph Node Biopsy (SLNB) (ME-F) in the NCCN Guidelines for Melanoma: Cutaneous.
[h] See Systemic Therapy for Metastatic or Unresectable Disease (MELSYS-1) in the NCCN Guidelines for Melanoma: Cutaneous.
[i] Principles of Radiation Therapy (VM-A).
[j] Principles of Surgery (VULVA-C).
[k] For invasive melanoma, recommend at least 1-cm margins, if feasible, with cautionary measures to avoid disfigurement.

Note: All recommendations are category 2A unless otherwise indicated.

FOLLOW-UP/ SURVEILLANCE

- **Recommend groin nodal ultrasound for stage ≥ IB[l]**
  - **every 3–6 months for first 2 years**
  - **then every 6–12 months for years 3–5**
- **Consider:**
  - **CT scan every 3–12 months**
  - **FDG-PET/CT particularly in cases of high-risk disease every 3–12 months**
- **See Follow-up recommendations (ME-10 and ME-11) in the NCCN Guidelines for Melanoma: Cutaneous**

→ **Recurrence** →

TREATMENT FOR RECURRENCE

Depending on type of recurrence, see Treatment of Recurrence pages in the NCCN Guidelines for Melanoma: Cutaneous

[l] Nodal ultrasound assessment for melanoma requires specific radiologic expertise. Criteria concerning for early melanoma nodal involvement include the following: hypoechoic island(s) in the cortex, asymmetrical focal cortical thickening, and peripheral vascularity, particularly when there is detectable perfusion to the area of cortical thickening. Core biopsy or FNA of suspicious LNs should be directed to the atypical area(s) within the cortex identified on ultrasound.

- van Akkooi ACJ, et al. Ann Surg Oncol 2010;17:660-662.
- Voit CA, et al. J Clin Oncol 2009;27:4994-5000.
- Voit CA, et al. Melanoma Res 2016;26;267-271.
- Faries MB, et al. N Engl J Med 2017;376:2211-2222.
- Bartlett EK, et al. Br J Surg 2020;107:1480-1488.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

VULVAR MELANOMA

- **Consider RT in medically inoperable patients or patients with symptomatic gross metastatic disease unresponsive to other therapies. RT can be considered for adjuvant therapy in situations where recurrent disease may cause excessive morbidity.**
- **Advanced techniques such as IMRT and image-guided RT (IGRT) should be used to maximize dose to the target and minimize dose to the normal tissues.[1,2]**
- **Contouring guidelines for vulvar melanoma are not available; however, the general guidelines for vulvar cancer are adaptable for this purpose.[3]**

- **Definitive Therapy (Unresectable or recurrent disease, treated with primary RT)**
  - **PTV high risk (primary tumor plus involved regional nodes) should receive a goal equivalent dose in 2 Gy fractions (EQD2) of 65–75 Gy, respecting normal tissue tolerance.**
  - **PTV low/intermediate risk (regions suspected to have subclinical disease) should receive a goal EQD2 dose of 44–55 Gy.**
  - **Interstitial brachytherapy is generally not used, except in highly selected cases with specialized care.**

- **Adjuvant Therapy (Postoperative RT)**
  - **May be considered for close or positive margins where re-resection may be too morbid.**
  - **Interval from surgery to RT is ideally <6 weeks unless adjuvant systemic therapy is given first, or for delayed wound healing.**
  - **Elective nodal radiation may be considered for any LN >3 cm, ENE, or ≥3 positive nodes.**

- **Dosing Regimens**
  - **More hypofractionated regimens may be chosen for smaller volume radiation. If primary and nodal volumes are targeted, then the more protracted courses will give less long-term toxicity, particularly for vulvar disease.**
  - **Optimal doses are not well-established, but potential regimens include:**

Vulvar Melanoma	Definitive Therapy
EBRT alone	PTV low/intermediate risk • 44–50 Gy (2 Gy/fraction) or • 55–63 Gy (1.8 Gy/fraction) PTV high risk • 66 (2.2 Gy/fraction) or • 70 Gy (2 Gy/fraction)

Vulvar Melanoma	Adjuvant Therapy
EBRT alone	Recommend doses on lower range (45–55 Gy) for elective nodal basins, middle range (50–55 Gy) for close margins, and higher range (55–65 Gy) for positive margins/ECE. • Simultaneous integrated boost (SIB) to nodes may be used to achieve an EQD2 of 66–70 Gy to gross disease. • Stereotactic body radiotherapy (SBRT) is often used in the treatment of melanoma given its relative radioresistance, however, is typically not a favored approach for a primary vulva site due to concern for toxicity. • 54–63 Gy (1.8 Gy/fraction), or • 44–50 Gy (2 Gy/fraction), or • 27–30 Gy (5.4–6 Gy/fraction) twice per week or every other day (for small volumes), or • 48 Gy (2.4 Gy/fraction),[4] or • 60–66 Gy (2 Gy/fraction) in 30–33 fractions over 6–7 weeks[5]

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF RADIATION THERAPY

VAGINAL MELANOMA

- RT (EBRT and/or brachytherapy) can be considered due to the potential morbidity of surgical resection.
- Advanced techniques such as IMRT, IGRT, and interstitial brachytherapy should be used to maximize dose to the target and minimize dose to the normal tissues.[1,2]
- MRI guidance is recommended for both initial simulation and especially at the time of brachytherapy. During the initial MRI simulation, water-soluble intravaginal gel can be very helpful at more specifically delineating the degree of mucosal involvement.
- Contouring guidelines are not available for vaginal melanoma; however, for vulvar cancer can be adapted to include inguinal coverage when there is involvement of the distal half,[3] and vaginal cancer/recurrence guidelines can be adapted for brachytherapy planning.[6,7]

- Definitive Therapy (Unresectable or recurrent disease, treated with primary RT)
  - PTV high risk (primary tumor plus involved regional nodes) should receive a goal EQD2 dose of 70–90 Gy, respecting normal tissue tolerance. Lower dose ranges (70–80 Gy) are used for distal disease due to higher radiation sensitivity of the distal vagina. Higher dose ranges (80–90 Gy) are used for apical/proximal diseases.
  - PTV low/intermediate risk (regions suspected to have subclinical disease) should receive a goal EQD2 dose of 44–55 Gy.
  - In non-melanoma vaginal cancers, brachytherapy with either interstitial or intracavitary techniques is the preferred approach to escalate dose to the gross vaginal disease and can similarly be used in vaginal melanoma when surgical resection is deemed too morbid, though data are limited.
  - For definitive therapy dosing regimens, see VM-A (3 of 7).
    - ◊ For OAR Constraints for Cumulative EBRT + Brachytherapy dosing, see VM-A (4 of 7).

- Adjuvant Therapy (Postoperative RT)
  - May be considered for close or positive margins where re-resection may be too morbid.
  - Interval from surgery to RT is ideally <6 weeks unless adjuvant systemic therapy is given first, or for delayed wound healing.
  - Elective nodal radiation may be considered for any LN >3 cm, ENE, or ≥3 positive nodes.[8]
  - For adjuvant therapy dosing regimens, see VM-A (5 of 7).

References Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

VAGINAL MELANOMA (continued)

- **Dosing Regimens for Definitive Therapy**
  - **More hypofractionated regimens may be chosen for smaller volume radiation. If primary and nodal volumes are targeted, then the more protracted courses will give less long-term toxicity.**
  - **Optimal doses are not well-established, but potential regimens include:**

Vaginal Melanoma	Definitive Therapy
EBRT alone (for distal primaries, brachytherapy generally preferred for proximal/apical disease)	PTV low/intermediate risk • 44–50 Gy (2 Gy/fraction) or • 54–63 Gy (1.8 Gy/fraction) PTV high risk • 66 (2.2 Gy/fraction) or • 70 Gy (2 Gy/fraction)
EBRT + brachytherapy boost	EBRT dose • 44–50 Gy (2 Gy/fraction) or • 54–63 Gy (1.8 Gy/fraction) Brachytherapy Dose • 4.5–6 Gy x 5 fractions • 7 Gy x 4 fractions • 8–9 Gy x 3 fractions Lower dose ranges are used for distal disease due to higher radiation sensitivity of the distal vagina. Higher dose ranges are used for apical/proximal disease. For OAR Constraints for Brachytherapy, see table on VM-A (4 of 7)
Brachytherapy alone (small primaries or in situ disease)	Potential brachytherapy regimens: • 5 Gy x 10 fractions • 6 Gy x 8 fractions • 8 Gy x 5 fractions

For Vaginal Melanoma, adjuvant therapy, see VM-A (5 of 7)

References Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINTS FOR BRACHYTHERAPY CUMULATIVE WITH EBRT

VAGINAL MELANOMA (continued)

- **Brachytherapy (Cumulative with EBRT for definitive therapy)**
  - **Total dose, including any EBRT is based on data from cervical cancer. Note that vaginal point doses are not included, but 200% isodose volumes should be limited within the vaginal wall to reduce the risk of necrosis.**

Organs at Risk	Ideal Dose Constraint (Gy)($EQD2_3$)	Maximum Dose Constraint (Gy)($EQD2_3$)	ICRU Point (Gy)($EQD2_3$)
Rectum	< 65 D2 cc	< 75 D2 cc	< 65 point dose
Bladder	75–80 D2 cc	< 90 D2 cc	< 75 point dose
Sigmoid	< 70 D2 cc	< 75 D2 cc	—
Bowel	<70 D2 cc	< 75 D2 cc	—

For Vaginal Melanoma, adjuvant therapy, see VM-A (5 of 7).

Note: All recommendations are category 2A unless otherwise indicated.

References Continued

PRINCIPLES OF RADIATION THERAPY

VAGINAL MELANOMA (continued)

- **Dosing Regimens for Adjuvant Therapy**
  - **More hypofractionated regimens may be chosen for smaller volume radiation. If primary and nodal volumes are targeted, then the more protracted courses will give less long-term toxicity.**
  - **Optimal doses are not well-established, but potential regimens include:**

Vaginal Melanoma	Adjuvant Therapy (Postoperative RT – less frequent due to the general inoperability of this disease)
EBRT alone	Recommend doses on lower range (45–55 Gy) for elective nodal basins, middle range (50–55 Gy) for close margins, and higher range (55–65 Gy) for positive margins/ECE. • 54–63 Gy (1.8 Gy/fraction),[9] or • 44–50 Gy (2 Gy/fraction), or • 27–30 Gy (5.4–6 Gy/fraction) twice per week or every other day (for small volumes),[8,10] or • 48 Gy (2.4 Gy/fraction),11 or • 60–66 Gy (2 Gy/fraction) in 30–33 fractions over 6–7 weeks[4,9]
EBRT + brachytherapy	EBRT • 50 Gy in 25 fractions or • 48 Gy in 20 fractions Brachytherapy Boost (close or positive margins)[a] • 6 Gy x 2–4 fractions at the vaginal surface • 5.5 Gy x 2–3 fractions at 5-mm depth • 7 Gy x 1–2 fractions at 5-mm depth
Brachytherapy alone (generally lower dose regimens)	Vaginal Surface Dose Regimens[a] • 6 Gy x 6–8 fractions • 5.7 Gy x 8 fractions • 8 Gy x 5 fractions 5-mm Depth Dose Regimens[a] • 7 Gy x 3 fractions • 5.5 Gy x 4 fractions

[a] Prescribing to the surface or 5-mm depth is a general institutional preference. When comparing regimens, for cylinders ~2.5–3 cm, the surface dose is ~30% higher than the 5-mm dose.

References Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

PALLIATIVE REGIMENS

- **More hypofractionated regimens may be chosen for smaller volume radiation. If primary and nodal volumes are targeted, then the more protracted courses will give less long-term toxicity; however, they should be carefully balanced against the metastatic burden of disease and overall prognosis.[12]**
- **Optimal doses are not well-established, but potential regimens include:**

RT Dosing (Gy)	Fractionation	Duration
48–50	20 fractions	In over 4 weeks[10]
30	10 fractions	In over 2 weeks[11]
30–36	6 Gy/fraction	For small fields[5]

- **Distant Metastatic Disease: Refer to Principles of Radiation Therapy (ME-H 3 of 7 and 4 of 7) in the NCCN Guidelines for Melanoma: Cutaneous.**
- **Managing Systemic Therapy During Radiation: Refer to Principles of Radiation Therapy (ME-H 5 of 7) in the NCCN Guidelines for Melanoma: Cutaneous.**

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY
REFERENCES

[1] Adams G, Foote M, Brown S, Burmeister B. Adjuvant external beam radiotherapy after therapeutic groin lymphadenectomy for patients with melanoma: a dosimetric comparison of three-dimensional conformal and intensity-modulated radiotherapy techniques. Melanoma Res 2017;27:50-56.
[2] Mattes MD, Zhou Y, Berry SL, Barker CA. Dosimetric comparison of axilla and groin radiotherapy techniques for high-risk and locally advanced skin cancer. Radiat Oncol J 2016;34:145-155.
[3] Gaffney DK, King B, Viswanathan AN, et al. Consensus recommendations for radiation therapy contouring and treatment of vulvar carcinoma. Int J Radiat Oncol Biol Phys 2016;95:1191-1200.
[4] Foote MC, Burmeister B, Burmeister E, et al. Desmoplastic melanoma: the role of radiotherapy in improving local control. ANZ J Surg 2008;78:273-276.
[5] Strom T, Caudell JJ, Han D, et al. Radiotherapy influences local control in patients with desmoplastic melanoma. Cancer 2014;120:1369-1378.
[6] Schmid MP, Fokdal L, Westerveld H, et al; GEC-ESTRO GYN Working Group. Recommendations from gynaecological (GYN) GEC-ESTRO working group - ACROP: Target concept for image guided adaptive brachytherapy in primary vaginal cancer. Radiother Oncol 2020;145:36-44.
[7] Kamrava M, Leung E, Bachand F, et al. GEC-ESTRO (ACROP)-ABS-CBG consensus brachytherapy target definition guidelines for recurrent endometrial and cervical tumors in the vagina. Int J Radiat Oncol Biol Phys 2023;115:654-663.
[8] Chang DT, Amdur RJ, Morris CG, Mendenhall WM. Adjuvant radiotherapy for cutaneous melanoma: comparing hypofractionation to conventional fractionation. Int J Radiat Oncol Biol Phys 2006;66:1051-1055.
[9] Strojan P, Jancar B, Cemazar M, et al. Melanoma metastases to the neck nodes: role of adjuvant irradiation. Int J Radiat Oncol Biol Phys 2010;77:1039-1045.
[10] Ang KK, Peters LJ, Weber RS, et al. Postoperative radiotherapy for cutaneous melanoma of the head and neck region. Int J Radiat Oncol Biol Phys 1994;30:795-798.
[11] Henderson MA, Burmeister BH, Ainslie J, et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. Lancet Oncol 2015;16:1049-1060.
[12] Bibault JE, Dewas S, Mirabel X, et al. Adjuvant radiation therapy in metastatic lymph nodes from melanoma. Radiat Oncol 2011;6:12.
[13] Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. Int J Radiat Oncol Biol Phys 1991;20:429-432.
[14] Huguenin PU, Kieser S, Glanzmann C, et al. Radiotherapy for metastatic carcinomas of the kidney or melanomas: an analysis using palliative end points. Int J Radiat Oncol Biol Phys 1998;41:401-405.

Note: All recommendations are category 2A unless otherwise indicated.

Staging-Vulvar Cancer

Table 1. **International Federation of Gynecology and Obstetrics (FIGO)**
New (2021) FIGO staging for carcinoma of the vulva

FIGO Stage	Description
I	Tumor confined to the vulva and/or perineum.
	IA Tumor size ≤2 cm and stromal invasion ≤1 mm[a]
	IB Tumor size >2 cm or stromal invasion >1 mm[a]
II	Tumor of any size with extension to lower one-third of the urethra, lower one-third of the vagina, lower one-third of the anus with negative nodes
III	Tumor of any size with extension to upper part of adjacent perineal structures, or with any number of nonfixed, nonulcerated lymph node
	IIIA Tumor of any size with disease extension to upper two-thirds of the urethra, upper two-thirds of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases ≤5 mm
	IIIB Regional[b] lymph node metastases >5 mm
	IIIC Regional[b] lymph node metastases with extracapsular spread
IV	Tumor of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases
	IVA Disease fixed to pelvic bone, or fixed or ulcerated regional[b] lymph node metastases
	IVB Distant metastases

[a] Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumor-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion. (van den Einden LC, et al. Mod Pathol 2015;28:295-302; Skala SL, et al. J Low Genit Tract Dis 2020;24:265-271).
[b] Regional refers to inguinal and femoral lymph nodes.

*Reprinted from: Olawaiye AB, Cotler J, Cuello MA, et al. FIGO staging for carcinoma of the vulva: 2021 revision. Int J Gynecol Obstet 2021;155:43-47. https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.13880. Copyright 2021, with permission from International Federation of Gynecology and Obstetrics.

ABBREVIATIONS

3D-CRT	three-dimensional conformal radiation therapy
BUN	blood urea nitrogen
CBC	complete blood count
CIS	carcinoma in situ
CLIA	Clinical Laboratory Improvement Amendments
CPS	combined positive score
CTV	clinical target volume
dMMR	deficient mismatch repair
EBRT	external beam radiation therapy
ECE	extracapsular extension
ENE	extranodal extension
EUA	examination under anesthesia
EQD2	equivalent dose at 2 Gy
FDG	fluorodeoxyglucose
FISH	fluorescence in situ
FNA	fine-needle aspiration
GTV	gross tumor volume
H&E	hematoxylin and eosin
H&P	history and physical
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
IGRT	image-guided radiation therapy
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
ISH	in situ hybridization
LN	lymph node
LVSI	lymphovascular space invasion
MIS	melanoma in situ
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
NGS	next-generation sequencing
OSLD	optically stimulated luminescence dosimeter
PD-L1	programmed death ligand 1
PTV	planning target volume
SBRT	stereotactic body radiation therapy
SCC	squamous cell carcinoma
SIB	simultaneous integrated boost
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
TLD	thermoluminescent dosimeter
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high
VIN	vulvar intraepithelial neoplasia

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Vulvar Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Vulvar Cancer (V3.2024). Last updated: December 21, 2023

Table of Content

Overview

In 2023, an estimated 6470 individuals will be diagnosed with vulvar cancer, and 1670 deaths are expected from the disease.[1] Vulvar cancer accounts for 5% to 8% of gynecologic malignancies and median age of diagnosis is 68 years. Based on data from the SEER database, 5-year survival rates range from 85.6% for localized disease (stages I/II), to 47.5% for regional or locally advanced disease (stages III/IVA), and finally to 23.3% for patients with stage IVB (which includes patients with pelvic nodal disease).[2] Studies of the SEER database and the National Cancer Database (NCDB) have shown that treatment approaches/modalities vary considerably with sociodemographic factors such as race/ethnicity, age, and non-private insurance, particularly for individuals with advanced disease.[3,4]

Ninety percent of vulvar cancers are of squamous cell carcinoma (SCC) histology.[5] Risk factors for the development of vulvar neoplasia include increasing age, infection with human papillomavirus (HPV), cigarette smoking, inflammatory conditions affecting the vulva, and immunodeficiency. Most vulvar neoplasias are diagnosed at early stages.[6] Rarer histologies exist and include melanoma, extramammary Paget's disease, Bartholin gland adenocarcinoma, verrucous carcinoma, basal cell carcinoma, and sarcoma.[7]

The International Society for the Study of Vulvovaginal Disease (ISVVD) has revised the terminology used to characterize vulvar lesions over the years. In 2004, vulvar intraepithelial neoplasia (VIN) terminology was refined to include two types of lesions, usual-type VIN and differentiated VIN (dVIN).[8] Usual-type VIN was linked to persistent infection with carcinogenic strains of HPV, while dVIN was commonly associated with vulvar dermatologic conditions such as lichen sclerosus. In 2015, the ISVVD updated the description to three classes of vulvar lesions: 1) low-grade squamous intraepithelial lesion (LSIL) due to flat condyloma or HPV effect; 2) high-grade squamous intraepithelial lesions (HSIL, formerly considered usual-type VIN); and 3) dVIN.[9] The 2020 WHO Classification of Female Genital Tumors, VIN is now classified as HPV-associated or HPV-independent. HPV-associated VIN corresponds to low- and high-grade squamous intraepithelial lesion (SIL) similar to other anatomic sites in the anogenital tract.[10] HPV-independent VIN is associated with a faster rate of progression to invasive SCC. It is the less common form of VIN and is often associated with lichen sclerosus.

The histologic grade of SCC is not well-defined and can be subjective. HPV-associated SCC has a better prognosis than HPV-independent SCC. HPV-associated SCC frequently occurs in younger patients, is multifocal, is associated with classic VIN, and can be seen in conjunction with additional sites of lower genital tract squamous neoplasia. Immunohistochemistry (IHC) shows strong, diffuse, block-like positive nuclear and cytoplasmic staining with p16 and wild-type p53 (heterogeneous staining pattern). HPV-independent SCC is split into two main groups: those associated with *TP53* mutations and those with wild-type *TP53* status.[11] The p53 abnormal, HPV-independent SCC usually occurs in older patients, is unifocal, and is associated with dVIN by histological evaluation. IHC usually shows aberrant p53 staining and negative or weak p16 staining. The p53 abnormal SCCs have the worst clinical outcomes of the three molecular categories (HPV positive, HPV-negative/p53 mutant, and HPV-negative p53 wild type). Assessing the presence and depth of invasion in vulvar SCC can be challenging.

Estimates of the percentage of vulvar cancers attributable to HPV infection range from conservative estimates of 30% to up to 69%, with a meta-analysis reporting an HPV prevalence of 39.7%.[12-15] A recent meta-analysis showed the prevalence of HPV in vulvar cancer and VIN to be 39.1% and 76.1%, respectively. Of the HPV-positive disease, 78.1% were HPV-16, followed by HPV-33 in vulvar cancer. A similar trend was

observed in VIN. The prevalence of p16-positive vulvar cancer was 34.1% while it was 65.7% in VIN.[16] However, HPV infection is detected in 80% to 90% of patients with SIL. Historically, VIN has been diagnosed in younger patients (median age 45–50 years) while vulvar cancers have been diagnosed in older patients (median age 65–70 years).[17,18] Because a large majority of HPV-related vulvar cancers are associated with HPV-16 and HPV-18 strains, vaccination with currently available HPV vaccines may reduce the burden of HPV-related vulvar cancers in the future.[12,17]

By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. "Many exceptions to the rule" were discussed among the members of the panel during the process of developing these guidelines. Recommendations in the NCCN Guidelines are category 2A unless otherwise noted.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Vulvar Cancer an electronic search of the PubMed database was performed to obtain key literature in vulvar cancer published since the previous Guidelines update, using the following search terms: vulvar cancer or carcinoma of the vulva. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Diagnosis and Workup

These guidelines utilize the FIGO (International Federation of Gynecology and Obstetrics) staging system for carcinoma of the vulva which was updated in 2021[19] from the 2009 system. [20-23] The updated FIGO system has included a revised definition for depth of invasion, lymph node (LN) metastases definition, and allows the incorporation of findings from cross-sectional imaging.

The presentation of vulvar cancer can be widely varied. The majority of vulvar cancers are located in the labia majora. Other possible sites include the labia minora, clitoris, mons pubis, or perineum. In patients with HPV-negative tumors, vulvar cancer often presents as a single mass or ulcer on the labia majora or minora. In HPV-positive tumors, multifocal lesions and concurrent cervical neoplasia are more common.[17,18,24] Although many cases may be asymptomatic, pruritus and pain/irritation are common symptoms; vulvar bleeding or discharge may also occur. A majority of patients present with early-stage localized disease.[2]

Diagnosis is made through biopsy of all suspicious areas followed by pathologic review. The College of American Pathologists (CAP) protocol for vulvar carcinoma is a useful guide (https://documents.cap.org/protocols/Vulva_4.2.0.2.REL_CAPCP.pdf). This CAP protocol was revised in 2021.

Workup includes history and physical examination, complete blood count (CBC), and liver and renal function tests. In addition to vulva examination, evaluation of the vagina and cervix (including cytologic smears) should be emphasized due to the multifocal nature of squamous cell intraepithelial neoplasia. CT, PET/CT, and MRI may be used to delineate the extent of tumor and/or for treatment planning.[25-28] Examination-under-anesthesia (EUA) cystoscopy or proctoscopy should be considered as indicated. Appropriate patients should receive smoking cessation counseling, cervical HPV testing, and cytology testing. Consider HIV testing, especially in younger patients. Those with vulvar cancer and HIV should be referred to an HIV specialist; modifications to the recommended cancer treatments in these Guidelines should not be modified solely on the basis of HIV status. For patients with vulvar cancer who are ≥65 years, also see the NCCN Guidelines for Older Adult Oncology at www.NCCN.org.

Prognostic Factors

Historically, en bloc vulvectomy with wide margins was combined with complete inguinofemoral (IF) lymphadenectomy to treat vulvar SCC. While effective in promoting survival, this approach was associated with serious short- and long-term morbidity (eg, wound complications, lymphedema, decreased sexual function, adverse impacts on body image). The emergence of data on important prognostic factors in vulvar cancer informed the evolution of surgical staging and primary treatment.[24] Based on a retrospective review of 586 patients enrolled in Gynecologic Oncology Group (GOG) trials through 1984, independent predictors of survival included the presence and number of involved LNs and primary tumor size.[29] LN metastasis is considered the most important prognostic factor and determinant of treatment in vulvar cancer,[30,31] and extracapsular extension has been linked to poorer prognosis.[32-35] Factors that may be predictive of recurrence and/or survival include depth of invasion, pathologic margin distance, tumor thickness, and presence of lymphovascular space invasion (LVSI).[17,29,36-41] However, these findings are primarily derived from retrospective analyses. A systematic review of the collective data on prognostic factors for local recurrence in vulvar cancer concluded that the weight of each individual prognostic variable remained equivocal when compared to one another.[42]

Prognostic data have guided the shift towards more conservative primary tumor resection and regional LN management for early-stage disease.[43] The preferred surgical approach evolved towards vulvar-sparing

techniques with separate incisions for lymphadenectomy in patients who were clinically node negative.[24,44] Current surgical approaches involve tailored primary tumor resection and LN evaluation based on individual patient characteristics.[45,46] Data suggest that survival is not negatively impacted by less radical surgical approaches for early-stage cancers.[46]

Surgical Staging

Previously, the AJCC and the 2009 FIGO systems staged vulvar cancer according to extent of primary tumor (T), LN status (N), and distant metastasis (M). Clinical staging alone provides inadequate evaluation of LN involvement. Because LN metastasis is a key prognostic factor in vulvar cancer survival,[30,46] these systems used a hybrid surgical and clinical/pathologic approach for more accurate evaluation of nodal status. Complete staging using the existing system requires primary tumor resection and full IF lymphadenectomy. However, common practice has increasingly included the use of sentinel LN (SLN) biopsy in lieu of complete lymphadenectomy, as well as diagnostic imaging to determine extent of disease.[47,48] In the new 2021 staging system, the revisions have been made to allow imaging to be used to assign stage. For stage 1 disease, the new method for measurement of depth of invasion has been added, which is now measured from the basement membrane of the deepest, adjacent, dysplastic, tumor-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion. Stage IIIA now also includes the upper two-thirds of the urethra, upper two-thirds of the vagina, and bladder mucosa or rectal mucosa, which were previously part of stage IVA. Stage IIIA includes any number of LNs less than or equal to 5 mm and no longer includes LN metastasis in a single node greater than 5 mm; this is now considered stage IIIB. Stage IVA includes disease fixed to pelvic bone or fixed or ulcerated regional LN metastases, and stage IVB includes any distant metastases.[19]

Pathologic Evaluation

Surgicopathologic factors may be used to guide the extent of surgical staging and treatment decisions. Findings from pathologic assessment of the surgical specimen should be carefully documented, including procedure type (ie, partial or total vulvectomy) and depth of procedure (ie, superficial or skinning, simple, or radical). Important elements of primary tumor evaluation include tumor site; size (in multiple dimensions); number of tumor foci; histologic type and grade; depth of stromal invasion; surgical margin status; and the presence of LVSI. When resected, the number of LNs with isolated tumor cells, micrometastases, and macrometastases should be recorded. If SLN mapping is performed, SLNs should undergo ultrastaging for detection of low-volume metastasis. Other important factors include tumor involvement of tissues/organs such as the vagina, urethra, anus, bladder mucosa, rectal mucosa, and pelvic bone. Mismatch repair (MMR), microsatellite instability (MSI), programmed death ligand 1 (PD-L1), neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion, and tumor mutational burden (TMB) testing may also be considered for treatment planning purposes in patients with recurrent, progressive, or metastatic disease. Additional testing to determine HPV status is recommended. Various methods can be used to detect HPV including detection of overexpressed p16 via IHC, and HPV-specific polymerase chain reaction (PCR) and in situ hybridization (ISH) techniques (for viral mRNA and DNA detection). The NCCN Guidelines recommend p53 IHC to determine p53 status. Evaluation of p53 IHC in vulvar SCC may be challenging and has unique features compared to p53 staining patterns encountered in ovarian and endometrial cancers.[49]

Primary Tumor Resection

Depending on the size and extent of the primary tumor, simple partial/total vulvectomy or radical partial/total vulvectomy may be required. No prospective data are available to compare outcomes between these resection techniques; however, retrospective data suggest no difference in

recurrence and/or survival.[50-52] Both surgical approaches involve resection of approximately a 1- to 2-cm radial margin of grossly normal tissue and to the deep fascia or a minimum of a 1-cm deep margin.

Vulvar cancer is associated with significant risk of local recurrence, and data demonstrate tumor margin status to be a significant prognostic factor.[36,39,53] A review identified 4-year recurrence-free rates of 82%, 63%, and 37% for patients with negative, close, and positive margins, respectively (P = .005). The highest risk of recurrence was associated with margins less than or equal to 5 mm.[54] The goal of primary tumor resection is complete removal with negative pathologic margins. The definition of a negative margin continues to evolve, and more data confirm the importance of a negative margin but put less emphasis on the actual distance (in mm) of the margin. In the setting of close or positive tumor margins, re-resection to obtain negative margins or adjuvant local radiation therapy (RT) are options.[36,55] In a study, tumor-free margins of at least 2 mm were associated with lower local recurrence risk.[40]

The risk-benefit ratio and morbidity of each approach must be weighed and individualized for each patient. Evidence supports improved recurrence rates and survival with re-resection or adjuvant external beam RT (EBRT) to the primary site.[56] However, for close or positive margins involving the urethra, anus, or vagina, re-resection may incur significant morbidity and negatively impact patient quality of life. Re-resection may also be inappropriate for patients with close or positive margins who have inguinal node involvement requiring adjuvant treatment with EBRT ± concurrent chemotherapy.

Lymph Node Evaluation

Because LN status is the most important determinant of survival in vulvar cancer, careful evaluation and determination of nodal status is paramount. LN resection is performed through a separate incision from the primary tumor and may entail ipsilateral or bilateral IF lymphadenectomy, or SLN biopsy in select cases. IF lymphadenectomy involves removal of superficial inguinal and deep femoral LN. Further emphasizing the importance of adequate IF lymph node (IFLN) evaluation and treatment at initial presentation, it has been widely reported that subsequent groin relapses are rarely amenable to successful secondary treatment.

Lymphadenectomy in patients with clinically negative groin nodes is informed by the size and location of the primary tumor. Because the risk of LN metastasis is less than 1% in patients with stage IA primary disease,[45] lymphadenectomy or SLN evaluation can be omitted in patients with stage IA primary disease with clinically negative groins. However, IF lymphadenectomy is recommended for patients with stage IB/II disease because the risk of nodal metastasis is estimated at greater than 8% for stage IB and even higher for stage II tumors.[45] For primary vulvar tumors less than 4 cm in diameter, located at least 2 cm from the vulvar midline, with clinically negative IFLNs, ipsilateral IF lymphadenectomy or SLN biopsy are appropriate.[57,58] However, bilateral LN evaluation (IF lymphadenectomy or SLN biopsy, if indicated) is recommended for patients with primary tumors that are within 2 cm of, or crossing, the vulvar midline.[58] Lymphadenectomy for stage III/IV disease is individualized, and integrated with combined modality approaches.

SLN Biopsy

Reported rates of postoperative morbidity with unilateral or bilateral IF lymphadenectomy are high. An estimated 20% to 40% of patients have wound complications and 30% to 70% of patients experience lymphedema.[59-61] Studies have begun to investigate whether complete IF lymphadenectomy could be safely avoided in patients who are determined to have a negative SLN. Several prospective multicenter trials have evaluated the feasibility, safety, validity, and risk of groin recurrences with SLN biopsy in early vulvar cancer.

The safety and accuracy of SLN assessment was examined in a multicenter observational study (GROINSS-V I) of 403 females with primary vulvar tumors less than 4 cm. IF lymphadenectomy was omitted if SLN(s) were negative on ultrastaging. With a median follow-up period of 35 months (24-month minimum), groin recurrences were detected among 6 of 259 patients (2.3%) with a unifocal primary tumor and negative SLN. The 3-year survival rate was 97%, leading to the conclusion that a negative SLN in this patient population provided sufficient management of the groin(s). Short- and long-term morbidity was reduced if the SLN only was removed compared with SLN removal followed by full groin lymphadenectomy.[62]

In GOG 173, 452 females (with vulva-confined primary tumors 2–6 cm, at least 1-mm invasion, and clinically node negative) underwent SLN mapping and biopsy followed by IF lymphadenectomy. SLNs were identified in 418 females, and 132 females were node positive (including 11 false-negative nodes). SLN biopsy had a sensitivity of 91.7%, negative predictive value of 96.3%, and false-negative predictive value of 3.7% overall (2% for primary tumors <4 cm).[63]

A subgroup analysis of the AGO-CaaRE-1 study compared outcomes of patients with tumors less than 4 cm who underwent radical groin lymphadenectomy or sentinel node lymphadenectomy with negative findings for LN/SLN metastasis (n = 556). The radical groin lymphadenectomy cohort had larger tumor diameter (20 mm vs. 13 mm; $P < .001$) and greater depth of invasion (4.0 mm vs. 3.0 mm; $P = .002$), but isolated groin recurrence rates did not differ between the groups. Multivariate analysis controlling for tumor characteristics such as diameter, depth of invasion, grade, and LVSI revealed no statistical differences in progression-free survival (PFS) and overall survival (OS) between the radical and sentinel node lymphadenectomy cohorts.[64]

A systematic review and meta-analysis of the cumulative data on SLN biopsy revealed a per-groin detection rate of 87% when using dual tracers, and a false-negative rate of 6.4%. When comparing IF lymphadenectomy, superficial IF lymphadenectomy, and SLN biopsy, recurrences rates were 1.4%, 6.6%, and 3.4% in patients deemed node-negative by the surgical groin approach used, respectively.[65]

The GROINSS-V I observational study also evaluated patients with positive SLNs. Within the 135 of 403 patients who had positive SLNs (33%), investigators examined the relationship between size of SLN metastasis and risk of non-sentinel node disease among 115 patients who underwent IF lymphadenectomy following detection of positive sentinel nodes. Risk of non-SLN involvement increased steadily with the size of SLN metastasis, beginning at 4.2% with detection of isolated tumor cells and increasing to 62.5% with SLN metastases greater than 10 mm, suggesting no disease threshold below which further treatment of an SLN-positive groin could be safely omitted. Disease-specific survival (DSS) was worse among those with SLN metastases greater than 2 mm versus less than or equal to 2 mm (69.5% vs. 94.4%, $P = .001$).[66] Patients undergoing SLN biopsy reported less treatment-related morbidity compared with those undergoing IF lymphadenectomy.[67]

Long-term follow-up of the GROINSS-V I cohort compared outcomes of SLN-positive patients who underwent completion IF lymphadenectomy with those of SLN-negative patients (no IF lymphadenectomy). At a median follow-up of 105 months, the data revealed a 5- and 10-year local vulvar recurrence rate of 24.6% and 36.4% for SLN-negative patients, and 33.2% and 46.4% for SLN-positive patients ($P = .03$). The isolated groin recurrence rate was 2.5% for SLN-negative patients and 8.0% for SLN-positive patients at 5 years, despite more radical treatment in the latter group. DSS at 10 years was 91% in the SLN-negative group and 65% in

the SLN-positive group (*P* < .0001), again attesting to the prognostic significance of groin nodal involvement.[68]

The GROINSS-V II/GOG 270 observational study (NCT01500512) compared the safety of IF radiotherapy with that of IF lymphadenectomy among patients with SLN metastases.[69] The trial further evaluated the treatment-related morbidity (short and long term) with radiotherapy in these patients. Among 322 patients with metastatic SLN, 160 had micrometastases (≤2 mm) and 162 patients had macrometastases (>2 mm). Among 160 patients with SLN micrometastases, 126 received IF radiotherapy, with an ipsilateral isolated groin recurrence rate at 2 years of 1.6%. In 162 patients with SLN macrometastases, the isolated groin recurrence rate at 2 years was 22% in those who underwent radiotherapy, and 6.9% in those who underwent IFL (*P* =.011). Treatment-related morbidity after radiotherapy was less frequent compared with IF lymphadenectomy.

The ongoing GROINSS-V III/NRG-GY024 phase 2 study is investigating the feasibility and safety of replacing IF lymphadenectomy with chemoradiation in patients with early-stage vulvar cancer with a macrometastasis and/or extracapsular extension in the sentinel node.[70]

Panel Recommendations

In the current version of the Guidelines, the section on principles of surgery has been updated to include management of mapping based on tumor location in reference to midline structures of the vulva. For appropriate individuals, the panel considers SLN mapping and biopsy of the IFLN basin to be a reasonable alternative approach to decrease postoperative morbidity while maintaining a low rate of groin recurrences.[62,63,66]

Candidates for SLN biopsy should have clinically/radiologically negative groin nodes, unifocal primary tumor less than 4 cm, and no history of previous vulvar surgery.[65,66] Mapping and biopsy should be performed by a high-volume SLN surgeon using dual tracers (ie, radiocolloid and dye) to ensure the best detection rates.[63,65] The panel recommends complete IF lymphadenectomy if no ipsilateral SLN is detected. If the ipsilateral SLN is positive, completion lymphadenectomy or treatment of the affected groin is warranted. The contralateral groin should be evaluated surgically and/or treated with EBRT. In select cases of a single, small-volume, unilateral, positive inguinal node with a well-lateralized small primary tumor and depth of invasion less than or equal to 5 mm and with a clinically negative contralateral groin examination, a contralateral groin lymphadenectomy or radiation may be omitted.[71]

Primary Treatment

For the purposes of primary treatment, these guidelines provide recommendations by clinical stage, separating patients into those with early-stage (stage I; select stage II tumors), locally advanced (unresectable without removing proximal urethra/bladder/anus), and distant metastatic disease beyond the pelvis.

Early-Stage Disease

After careful clinical evaluation and staging, the standard primary treatment of early-stage vulvar cancer is conservative, individualized tumor excision with IFLN evaluation.[44,51,72-75] Clinicians should strive for primary tumor resection with oncologically appropriate margins of 1 to 2 cm if feasible.[36,39,53,55] See *Primary Tumor Resection* and *Lymph Node Evaluation* in this discussion. Although there are no prospective data comparing radical local incision to radical vulvectomy, existing data from retrospective analyses do not demonstrate a difference in recurrence or survival outcomes.[51,52]

Surgical dissection and RT have been evaluated for treatment of the groin in early-stage disease. Limited data suggest that primary groin radiation

results in less morbidity than surgical dissection.[76] However, surgical treatment of the groin (followed by tailored adjuvant RT if LN-positive) has been associated with lower groin recurrence rates and remains the preferred approach.[77] Primary radiation may have some benefit for those unable to undergo surgery.[78,79]

Panel Recommendations

For stage I tumors with less than or equal to 1 mm depth of invasion, the panel recommends simple partial vulvectomy; IFLN evaluation is not required due to the low risk of LN metastasis in these patients.[45,73,80-83] Patients should be observed following resection. If surgical pathology reveals greater than 1-mm invasion, additional surgery may be indicated.

In treatment for patients with stage IB (>1-mm invasion) or select stage II tumors, primary treatment is dictated by tumor location. Patients with lateralized lesions located greater than or equal to 2 cm from the vulvar midline should undergo radical partial vulvectomy accompanied by ipsilateral IFLN evaluation.[57,58,80] IF node evaluation can be performed through SLN biopsy or ipsilateral IF lymphadenectomy; the latter should be performed if no SLN(s) is/are detected. Adjuvant therapy is informed by primary tumor risk factors and nodal surgical pathology. Patients with anterior or posterior central vulvar lesions should undergo radical partial vulvectomy accompanied by bilateral IF node evaluation consisting of SLN biopsy or bilateral IF lymphadenectomy.[51,58,80] IF lymphadenectomy is required on side(s) for which sentinel nodes are not detected. Adjuvant therapy is informed by primary tumor risk factors and nodal surgical pathology. For lateralized and near midline tumors with unilateral SLN metastasis, unilateral groin treatment by either IF lymphadenectomy or RT is acceptable. For midline tumors with unilateral SLN metastasis, unilateral groin treatment can be performed if the contralateral groin has negative sentinel node or negative IF lymphadenectomy.[58,84]

Locally Advanced Disease

Historically, locally advanced vulvar cancers were treated primarily with radical surgeries such as en bloc radical vulvectomy with bilateral IF lymphadenectomy or pelvic exenteration. These surgeries resulted in some cures, but also led to significant postoperative complications, loss of function, and reduced quality of life.[24,85-87] Additionally, complete resection of locally advanced disease may be complicated by tumor fixed to vital organs or vessels, rendering the disease unresectable.[88] A shift to multimodality treatment was explored to improve organ preservation and reduce surgical treatment morbidity.[89] Preoperative RT was shown in some earlier studies to result in tumor debulking and reduce the extent of surgery required for locally advanced disease.[88,90-93] Subsequently, borrowing on experience from advanced cervical and anal cancers, chemotherapy typically has been added as a “radiosensitizer” when radiation is delivered in patients with advanced disease.

Chemoradiation

Research directly comparing treatment approaches for locally advanced vulvar cancers is limited. Data from small patient cohorts have shown a generally high response rate to chemoradiation among most patients with stage III/IVA disease, as well as the feasibility of resection for residual disease following chemoradiation. Following chemoradiation, at least partial tumor responses were noted among a wide majority of the patients in these cohorts,[94-98] with several studies revealing complete tumor responses among more than 60% of the cohort.[99-103]

Primary chemoradiation may confer a survival benefit over primary RT in vulvar cancer. OS after primary chemoradiation was superior to OS following primary RT in a series of 54 patients with locally advanced disease.[104] A similar survival benefit was reported in a study using NCDB data from patients who were not candidates for surgery, comparing cohorts who received primary chemoradiation (n = 999) or primary RT (n =

353). The chemoradiation cohort was younger with more advanced disease based on FIGO staging. Chemoradiation was associated with significantly higher 5-year OS than primary RT (49.9% vs. 27.4%, *P* <0.001) and multivariate analysis revealed a reduced hazard of death (hazard ratio [HR], 0.76; 95% CI, 0.63–0.91; *P* = .003).[105]

In the GOG 101 study, preoperative chemoradiation was examined in 73 patients with stage III/IV disease.[96] The study investigated whether chemoradiation allowed for less radical surgery in patients with T3 tumors and avoidance of pelvic exenteration in patients with T4 tumors. Only 3% of patients (2/71) had residual unresectable disease following chemoradiation, and preservation of urinary and/or gastrointestinal (GI) continence was possible in 96% of patients (68/71).

Two prospective studies from the GOG more closely examined the benefits of surgery after chemoradiation for patients with locally advanced disease. GOG 101 examined 46 patients with vulvar SCC and N2/N3 nodal involvement.[106] Subsequent surgery was performed on 38 patients with resectable disease after chemoradiation with cisplatin/5-fluorouracil (5-FU). Local control of nodal disease was achieved in 36 of 37 patients and for the primary tumor in 29 of 38 patients. The GOG 205 study examined the feasibility of surgery after chemoradiation with cisplatin in 58 patients with T3/T4 tumors that were initially unresectable by radical vulvectomy.[107] Complete clinical response was noted in 64% of patients (37 of 58), with pathologic complete response (pCR) in 78% (29 of 34) of patients undergoing surgical biopsy. Of the total population, approximately 50% achieved pCR after chemoradiation therapy. The high pCR rates have led many to believe that surgery can be avoided in patients with locally advanced tumors who achieve clinical complete responses.

A phase II, multicenter, prospective trial evaluated treatment feasibility, percentage of locoregional control, survival, and toxicity after locoregional radiotherapy combined with sensitizing chemotherapy with capecitabine in 52 patients with T2/T3 tumors.[108] Of the total patients, 58% had no evidence of disease at a median of 35 months. PFS was 58%, 51%, and 45%, and OS was 76%, 66%, and 52% at 1, 2, and 5 years, respectively. Most acute toxicity greater than or equal to grade 3 reported were related to skin/mucosa (54%) and pain (37%). Late toxicity greater than or equal to grade 3 was reported for skin/mucosa (10%), fibrosis (4%), GI incontinence (4%) and stress fracture or osteoradionecrosis (4%).

An analysis of NCDB data (2004–2012) compared outcomes of 2046 females with locally advanced vulvar cancer who received primary radiation (RT or chemoradiation), or preoperative radiation (RT or chemoradiation) followed by surgery. Patients who underwent surgery after RT/chemoradiation had longer OS than patients who underwent primary RT/chemoradiation without subsequent resection (57.1% vs. 41.7% at 3 years, respectively; *P* < .001). However, multivariate analysis revealed a radiation dose-dependent effect, and survival was not significantly worse if the dose exceeded 55 Gy. With sufficient RT dose and concurrent chemotherapy, the primary RT cohort had comparable survival to the group who underwent lower-dose preoperative RT/chemoradiation followed by surgery.[109]

A 2011 Cochrane database review of the existing randomized controlled trial data on 141 females with locally advanced vulvar SCC revealed no difference in OS when comparing primary surgery to primary or neoadjuvant chemoradiation.[110] However, the data did not allow for broad conclusions to be drawn regarding treatment-related quality of life and adverse events. An earlier Cochrane database review of five non-randomized trials suggested that patients with unresectable primary disease and those requiring exenteration may benefit from neoadjuvant chemoradiation if disease was rendered resectable or requiring less radical surgery.[111]

The combination regimen used for radiosensitization was most commonly cisplatin/fluorouracil,[96,97,99,101,102] but also included fluorouracil/mitomycin C[95,98,103] or single-agent therapy.[100,107] The selection of radiosensitizing chemotherapy is often based on extrapolation of findings from cervical, anal, or head and neck cancer.

Panel Recommendations

Patients with locally advanced tumors (unresectable without removing proximal urethra/bladder/anus) should undergo radiologic imaging to examine potential nodal involvement. The panel recommends that all patients with locally advanced disease receive EBRT with concurrent chemotherapy. IF lymphadenectomy may be used to assess nodal metastasis and inform RT treatment planning.

If IF lymphadenectomy is not performed, or if positive IFLNs are found during the procedure, EBRT coverage should include the primary tumor, groin, and pelvic nodes. If no positive nodes are detected following IF lymphadenectomy, EBRT with concurrent chemotherapy should be provided with RT coverage of the primary tumor, with or without selective coverage of IFLNs.

Patients with radiographically suspicious nodes (including those with pelvis-confined metastases) should be evaluated for IF lymphadenectomy. If IF lymphadenectomy is not performed, fine-needle aspiration (FNA) of enlarged LNs can be considered. Patients should receive EBRT and concurrent chemotherapy; EBRT coverage should include the primary tumor, IF nodes, and pelvic nodes. Selective IFLN RT coverage can be considered if lymphadenectomy reveals no positive LNs.

Agents recommended by the panel for chemoradiation include cisplatin (preferred) and carboplatin if the patient is intolerant to cisplatin. The panel also lists cisplatin/fluorouracil under “other recommended regimens.”[112]

In addition, if cisplatin or carboplatin are unavailable, the panel has included capecitabine/mitomycin, gemcitabine, and paclitaxel as options that may be considered under the “other recommended regimens” category. These radiosensitizers were added based on a few early-phase studies extrapolated from cervical cancer that have shown their efficacy and tolerability when administered concomitantly with radiation.[113-116]

Metastasis Beyond the Pelvis

The NCCN Panel recommends primary treatment options for extra-pelvic metastatic disease including EBRT for control of locoregional disease and symptom palliation, and/or systemic therapy. Best supportive care is also an alternative in this setting. Data on systemic treatments for vulvar cancer with distant metastasis are extremely limited.[117-119] Treatment regimens are often extrapolated from agents that are active against advanced cervical cancer. See the section on *Systemic Therapy for Recurrent/Metastatic Disease* in this discussion for information about specific regimens.

Adjuvant Therapy

Due to the rarity of vulvar cancer, especially advanced disease, prospective randomized trials on adjuvant therapy are extremely limited. Much of the common adjuvant treatment approaches have been drawn from studies describing heterogenous, often-individualized treatment approaches, or extrapolated from effective adjuvant therapies for cervical and anal cancers.

Adjuvant RT and Chemoradiation

Although it is commonly accepted that LN involvement is a critical prognostic factor in vulvar cancer, the optimal patient selection criteria and adjuvant therapy regimens to address nodal disease continue to be determined.[120] As previously emphasized, it is crucial to prevent metachronous groin relapses, as these often prove refractory to secondary management and are often ultimately fatal.

Early randomized trial data on adjuvant RT were published from GOG 37, which enrolled 114 patients with IF node-positive vulvar cancer after radical vulvectomy and bilateral IF lymphadenectomy.[121,122] Patients were randomized to receive pelvic lymphadenectomy or adjuvant RT to the groin/pelvis. Two- and 6-year survival were superior in the adjuvant RT group, but the most significant survival benefits were observed among patients with greater than or equal to 2 positive IF nodes or those with fixed ulcerative IF nodes. Long-term follow-up (median = 74 months) revealed higher rates of disease-related death for the group receiving pelvic node resection compared with pelvic/groin RT (51% vs. 29%; HR, 0.49; *P* = .015).[122]

A study using SEER-Medicare–linked data examined outcomes for 444 older patients (aged ≥66 years; median age 78) with node-positive vulvar cancer who underwent adjuvant RT. Compared to surgery alone, better disease outcomes were associated with adjuvant RT when the following metrics were met: completion of at least 20 fractions, treatment duration of less than 8 weeks, and less than 1 week of intra-treatment break. However, only half of the cohort that received RT met these treatment benchmarks.[123]

There are conflicting data on the benefit of adjuvant RT in patients with a single positive LN. Some studies in patients with a single positive LN have reported no benefit of adjuvant RT in this setting.[124,125] However, examination of SEER data from 208 patients with stage III, single node-positive vulvar SCC revealed significant improvements in 5-year DSS with the addition of adjuvant RT compared with those receiving no RT.[126] The survival benefit was more pronounced among patients who underwent less extensive lymphadenectomy (≤12 nodes excised).

In a case series of 157 patients, disease-free survival (DFS) at 2 years was 88% in node-negative patients, but 60%, 43%, and 29% in patients with 1, 2, and greater than 2 positive nodes. The number of involved nodes negatively impacted prognosis in patients receiving no adjuvant RT, but among patients receiving adjuvant RT to the groin/pelvis, the number of metastatic nodes did not harm prognosis.[127]

The large, multicenter, retrospective AGO-CaRE-1 study reported significant survival benefits in node-positive patients receiving adjuvant RT or chemoradiation (3-year PFS of 39.6% vs. 25.9%, *P* = .004; 3-year OS of 57.7% vs. 51.4%, *P* = .17).[125] RT coverage most commonly included the groin and pelvis ± coverage of the vulva, with a smaller subset receiving coverage to the groin ± vulvar coverage. Again, the benefits of adjuvant RT were most clear for patients with greater than or equal to 2 positive LNs.

An examination of data from the NCDB supported the addition of chemotherapy to RT in the adjuvant setting. Among 1797 patients with node-positive vulvar cancer, 26.3% received adjuvant chemotherapy in addition to RT after primary surgery. Adjuvant chemotherapy increased survival time and reduced mortality risk (44 months vs. 29.7 months; HR, 0.62; 95% CI, 0.48–0.79; *P* < .001).[128] Based on SEER data, outcomes of adjuvant RT were examined in 519 patients aged ≥66 years who received primary surgery for node-positive vulvar cancer. Adjuvant RT was associated with improved OS over surgery alone in this cohort of older females (HR, 0.71; 95% CI, 0.57–0.88; *P* = .002) along with a trend towards improved cause-specific survival (CSS) (HR, 0.79; 95% CI, 0.59–1.05; *P* = .11).[129] Parameters for delivery of RT were important among this cohort; 3-year OS and CSS were significantly improved in patients who received greater than or equal to 20 fractions (3-year OS: 34% vs. 26%, *P* = .008; 3-year CSS: 48% vs. 37%, *P* = .03).

Research has also examined the role of adjuvant RT to the primary tumor site. Studies have indicated that isolated primary site recurrences may be addressed effectively by subsequent surgery, or that late recurrences may actually represent secondary tumors. The benefit of adjuvant RT to the

vulva in patients with close/positive surgical margins has also been investigated.[130] Among patients with close/positive surgical margins at the primary site, 5-year OS was significantly improved by the addition of adjuvant RT to the primary site (67.6% vs. 29%; HR, 0.36; *P* = .038). Patients receiving adjuvant RT for close/positive margins had a similar 5-year OS to those with negative margins. A retrospective study examined the association of RT dose with vulvar recurrence, revealing lower risk of recurrence in patients receiving doses of greater than or equal to 56 Gy compared with those receiving less than or equal to 50.4 Gy.[54]

Panel Recommendations

For patients with early-stage disease (stage I) and a depth of invasion less than or equal to 1 mm, observation is appropriate following primary surgery if negative margins are present, and the patient does not have any primary risk factors. Risk factors that may require adjuvant EBRT to the primary site are close tumor margins, LVSI, tumor size, depth of invasion, and pattern of invasion (spray or diffuse). Those with positive margins should undergo re-excision, or if unresectable without removing proximal urethra/bladder/anus, adjuvant EBRT. After re-excision, the panel recommends that patients with negative margins undergo observation or risk-factor-dependent EBRT; those with continued positive margins after re-excision should all undergo EBRT.[130]

For patients with stage IB (>1 mm invasion) and stage II disease, surgical evaluation of the groin is indicated in addition to primary site surgery. Nodal status is an important determinant of adjuvant therapy recommendations. For patients with a negative SLN or negative IFLNs, observation can be considered.[62,131-134] Adjuvant therapy is warranted if the SLN or IFLNs contain metastases. Adjuvant therapy for patients with SLN involvement includes: 1) RT ± concurrent chemotherapy; or 2) completion IF lymphadenectomy followed by EBRT ± concurrent chemotherapy. Adjuvant therapy for patients who have positive IFLNs detected during IF lymphadenectomy includes EBRT (category 1) ± concurrent chemotherapy. Chemoradiation is strongly recommended for patients with two or more positive IFLNS or a single IFLN with greater than 2-mm metastasis.[121,125] For patients with locally advanced disease, adjuvant therapy decisions should be made based on clinical evaluation of treatment response after EBRT with concurrent chemotherapy (potentially preceded by IF lymphadenectomy). These guidelines provide adjuvant therapy recommendations based on whether patients are clinically negative or positive for residual tumor at the primary site and in the groin. Patients with no clinical evidence of residual tumor after EBRT with concurrent chemotherapy should undergo surveillance. Biopsy of the tumor bed can also be considered to confirm pCR. Patients with residual tumor should be considered for resection. In the case of positive margins on resection, providers should consider additional surgery, additional EBRT, and/or systemic therapy, or best supportive care. For unresectable residual disease, providers should consider additional EBRT and/or systemic therapy, or best supportive care.

Surveillance

Most recurrences of vulvar cancer occur within the first 1 to 2 years, although recurrences beyond 5 years have been observed in a significant subset of patients.[135,136] Accordingly, long-term follow-up is indicated. Definitive data on an optimal surveillance strategy are lacking.[137] However, the panel concurs with the Society of Gynecologic Oncology (SGO) recommendations for post-treatment surveillance.[138]

The recommended surveillance is based on the patient's risk for recurrence and personal preferences. History and physical examination are recommended every 3 to 6 months for 2 years, every 6 to 12 months for another 3 to 5 years, and then annually (see *Surveillance* in the NCCN Guidelines for Vulvar Cancer). Patients with high-risk disease can be

assessed more frequently (eg, every 3 months for the first 2 years) than patients with low-risk disease (eg, every 6 months).

Annual cervical/vaginal cytology tests, which may include HPV testing, can be considered as indicated for detection of lower genital tract dysplasia, although its value in detecting recurrent cancers is limited and the likelihood of detecting asymptomatic recurrence is low. In addition, the accuracy of these tests may be affected in patients who have received pelvic radiation as radiotherapy can induce changes in cellular morphology that may result in cytological misdiagnosis. Imaging (ie, chest/abdomen/pelvis CT, neck/chest/abdomen/pelvis/groin FDG-PET/CT, pelvic MRI) and laboratory testing (ie, CBC, blood urea nitrogen [BUN], creatinine) are recommended as indicated by suspicious examination findings or symptoms of recurrence.

Patient education regarding symptoms suggestive of recurrence or vulvar dystrophy is recommended, as well as periodic self-examination. Patients should also be counseled on healthy lifestyle, obesity, nutrition, exercise, and sexual health (including vaginal dilator use and lubricants/moisturizers). For information on these and other issues related to survivorship (ie, pain/neuropathy, fear of recurrence, depression), see the *Gynecologic Survivorship* section at the end of this document and the NCCN Guidelines for Survivorship (available at www.NCCN.org). Smoking cessation and abstinence should be encouraged; see the NCCN Guidelines for Smoking Cessation (available at www.NCCN.org).

If persistent or recurrent disease is suspected, patients should be evaluated using additional imaging studies and biopsy to confirm local and/or distant recurrence as outlined in the next section.

Treatment for Recurrent Disease

A multicenter case series evaluated the rate and patterns of recurrence among 502 patients, 187 (37%) of who developed a recurrent vulvar SCC. Just over half of recurrences were vulvar (53.4%), followed by inguinal (18.7%), multi-site (14.2%), distant (7.9%), and pelvic (5.7%). Survival rates at 5 years were 60% for vulvar recurrence, 27% for inguinal/pelvic, 15% for distant sites, and 14% for multiple sites.[31] While localized vulvar recurrences can be successfully addressed with subsequent surgery, some studies have suggested higher risk of cancer-related death.

Given the rarity of primary vulvar cancer, data for treating recurrences are even scarcer and no clear standard of care exists.[139] Treatment approach and patient outcomes depend on the site and extent of recurrent disease.[139,140] Isolated local recurrences can often be treated successfully with radical local excision,[31,136,141] and RT ± chemotherapy provided some degree of DFS in several studies.[92,93] A retrospective review evaluated patients with locoregional recurrences treated via chemoradiation, neoadjuvant chemotherapy, or RT alone. Five-year DFS and OS were around 20%; however, those with single-site recurrence and lesions less than or equal to 3 cm who received RT dose at or above 64.8 Gy remained disease-free at 5 years.[142] Conversely, another series noted decline in survival with the presence of nodal metastases, tumors greater than 3 cm, or high-grade lesions.[143] For central/large recurrences, pelvic exenteration has been shown to prolong survival when performed on carefully selected patients.[85,86,144] Regardless of treatment approach, prognosis for nodal recurrences was very poor.[136,141,143,145,146]

Panel Recommendations

If recurrence is suspected, the panel recommends workup for metastatic disease with imaging studies to include chest/abdominal/pelvis CT or neck/chest/abdomen/pelvis/groin FDG-PET/CT. Biopsy can be considered to confirm local and/or distant metastasis. Treatment recommendations for recurrent disease are outlined according to site of recurrence and previous therapies received.

Vulva-Confined Recurrence

If recurrence is clinically limited to the vulva with clinically negative nodes, and the patient did not receive prior RT, the panel recommends surgical and RT treatment pathways. Surgical recommendations include partial or total radical vulvectomy ± unilateral or bilateral IF lymphadenectomy. Pelvic exenteration can be considered for select cases with a central recurrence. Additional therapy is indicated by margin status and nodal status. Observation or EBRT is appropriate for negative margins and nodes. In patients with positive margins but no evidence of nodal involvement, options include re-excision or EBRT ± brachytherapy and/or concurrent chemotherapy (category 2B for chemotherapy). EBRT ± concurrent chemotherapy is recommended for patients with negative surgical margins but surgically positive IFLNs. In patients with both positive margins and surgically positive IFLNs, the panel recommends EBRT ± brachytherapy, concurrent chemotherapy, and/or re-excision as needed/appropriate.

Nonsurgical therapy for recurrence includes EBRT ± brachytherapy and/or concurrent chemotherapy. Resection can be considered for patients with gross residual tumor. When feasible, partial or total radical vulvectomy is also indicated for patients with vulva-confined recurrence who were previously irradiated. After treatment for recurrence, patients should undergo surveillance.

Confirmed Nodal or Distant Recurrence

For patients with multiple pelvic nodes, distant metastasis, or prior pelvic EBRT, the panel recommends systemic therapy and/or selective EBRT (if feasible) or palliative/best supportive care. If recurrence is limited to IF/pelvic LNs, resection should be considered for clinically enlarged and suspicious nodes. Resection followed by systemic therapy can be considered for select cases of isolated IF/pelvic recurrence that were previously irradiated. If no prior RT was given, then EBRT ± concurrent chemotherapy is appropriate. All patients should undergo surveillance following treatment for recurrence.

Systemic Therapy for Recurrent/Metastatic Disease

No standard systemic therapy regimens exist for treating advanced or recurrent/metastatic disease. Several reports provide anecdotal evidence for various regimens, at times extrapolating from regimens with known activity in advanced cervical and anal cancers and other SCCs. See the review articles by Reade et al and Mahner et al for an overview of systemic therapies that have been utilized to treat vulvar SCC.[112,139] Preferred, first-line regimens recommended by the panel for treating advanced, recurrent/metastatic disease include cisplatin/paclitaxel, carboplatin/paclitaxel, and cisplatin/paclitaxel/bevacizumab. Carboplatin/paclitaxel/bevacizumab is included as a category 2B regimen under the preferred, first-line options. Other recommended regimens include single-agents cisplatin and carboplatin.

Cisplatin is a commonly employed radiosensitizing agent in locally advanced vulvar cancer, and is recommended for single-agent or combination chemotherapy for treatment of metastatic disease.[88,147] Cisplatin/paclitaxel and cisplatin/paclitaxel/bevacizumab are preferred regimens based on extrapolation of randomized phase III trial data in advanced or recurrent/metastatic cervical cancer.[148,149]

Carboplatin is an alternative platinum agent active in metastatic cervical cancer that can be used as a single agent or in combination. A small series in 6 patients with advanced or recurrent/metastatic vulvar cancer noted limited clinical benefit of the combination regimen;[117] however, it has been included in these guidelines based on data from patients with advanced or recurrent/metastatic cervical cancer that suggest non-inferiority to cisplatin.[150,151]

For the second-line or subsequent treatment, the NCCN Panel has listed paclitaxel, erlotinib (category 2B for erlotinib), and cisplatin/gemcitabine (category 2B) as options.

Single-agent paclitaxel was modestly active in a phase II trial of 31 females with advanced, recurrent/metastatic vulvar cancer, generating a response rate of 14% and PFS of 2.6 months.[118] Erlotinib was studied in a phase II trial that included a cohort of females with metastatic disease. Short-duration responses were observed, with partial responses and stable disease noted in 27.5% and 40% of enrolled patients, respectively.[119] Cisplatin/gemcitabine is also included as a category 2B option extrapolating from cervical cancer data; however, findings from case reports have been mixed.[152,153]

In the recent Guidelines update, the NCCN Panel also included cemiplimab as a second-line or subsequent therapy option under "other recommended regimens." The recommendation of cemiplimab has been extrapolated from its efficacy shown in cervical cancer and in advanced cutaneous SCC. In a phase 2 trial with patients with metastatic cutaneous SCC, a response was observed in 28 out of 59 patients.[154] Median follow-up was 7.9 months. The phase 3, randomized, Empower-Cervical-1 clinical trial evaluated the efficacy of cemiplimab or investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) in patients with recurrent or metastatic cervical cancer who have progressed on prior therapy. The trial enrolled 608 patients who had previously received one or more lines of systemic therapy for recurrence; they were randomized to either receive cemiplimab or chemotherapy. The median OS and PFS were significantly longer in the cemiplimab arm than in the control arm (12 months vs. 8.5 months; HR, 0.69; 95% CI, 0.56–0.84; $P < .001$ and 2.8 vs. 2.9 months; HR, 0.75; 95% CI, 0.63–0.89; $P < .001$, respectively). Sixteen percent of the patients in the test arm achieved an OR (95% CI, 12.5–21.1) as compared to 6.3% (95% CI, 3.8–9.6) in the chemotherapy arm.[155]

Biomarker-directed systemic therapies are an emerging class of treatments that may be useful in patients with advanced or recurrent/metastatic cancer. Monoclonal antibodies that function as programmed cell death protein 1 (PD-1) inhibitors are one such example of these treatments. PD-1 functions as an immune checkpoint protein that promotes antitumor T-cell activity. Many tumors, including vulvar cancer, are known to overexpress PD-L1, which disrupts PD-1 function. Thus, blocking PD-L1/PD-1 binding restores T-cell–mediated antitumor activity.[156-158] An estimated 10% to 50% of vulvar cancers express PD-L1.[159,160]

Pembrolizumab is one such PD-1 inhibitor that may be effective in patients with vulvar cancer. A case study was published of a single patient with recurrent vulvar SCC who was treated with single-agent pembrolizumab, as part of a phase II basket clinical trial to evaluate efficacy and safety,[161] and had 30% reduction in tumor lesions before the treatment was discontinued due to grade 3 mucositis.[162] The single-arm phase II KEYNOTE-158 basket trial (NCT02628067) measured response to pembrolizumab monotherapy in patients with advanced solid tumors that progressed after standard-of-care systemic therapy.[163] Among 101 patients enrolled in the vulvar SCC cohort, median follow-up was 36 months. The overall response rate (ORR) was 10.9% overall, 9.5% in the PD-L1–positive population, and 28.6% among the PD-L1–negative population. Median PFS and OS were 2.1 and 6.2 months, respectively.[164] Pembrolizumab is FDA-approved for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1). The panel has added pembrolizumab as a recommended second-line, useful in certain circumstances option for PD-L1–positive advanced or recurrent/metastatic vulvar cancer.

Monoclonal antibodies targeting the PD-1 pathway may also be effective in tumors that have high TMB (TMB-H) or are deficient in MMR (dMMR)/have high levels of MSI (MSI-H). Of the 71 patients in the KEYNOTE-158 trial with advanced vulvar cancer, 12 had TMB-H tumors. The ORR for TMB-H vulvar cancer was approximately 17%, while the ORR for non–TMB-H disease was 3.4%.[165] The KEYNOTE-158 study authors also analyzed pembrolizumab response in 233 enrolled patients with non-colorectal MSI-H/dMMR tumors, one of which had vulvar cancer. ORR for the entire cohort was 34.3%. Median PFS was 4.1 months and median OS was 23.5 months.[166] Based on these data, the FDA expanded pembrolizumab's approval for treatment of TMB-H and MSI-H/dMMR tumors that progressed after prior therapy, regardless of tumor type.[167,168] Based on these additional data/FDA approvals, the panel also recommends pembrolizumab as a second-line, useful in certain circumstances option for patients with advanced or recurrent/metastatic vulvar cancer whose tumors are MSI-H/dMMR or TMB-H.

Nivolumab is another PD-1 inhibitor shown to have some efficacy in certain patients with vulvar cancer. The single-arm phase I/II CheckMate 358 trial (NCT02488759) measured response to nivolumab monotherapy in a small cohort of 5 patients with recurrent or metastatic vaginal or vulvar cancer who were HPV-positive or had an unknown HPV status. The 12- and 18-month OS rates for the combined cohort were 40% and 20%, respectively; 6-month PFS was 40%.[169] Based on these data, the panel added nivolumab as a second-line, useful in certain circumstances option for HPV-related advanced or recurrent/metastatic vulvar cancer.

NTRK gene fusions lead to constitutively active tropomyosin receptor kinases (TRKs), which in turn promote development and progression of cancer. Approximately 0.3% of solid tumors express *NTRK* gene fusions, although expression varies widely by cancer type.[170] Entrectinib and larotrectinib are broadly active TRK inhibitors that are effective in patients with a variety of advanced or metastatic *NTRK* fusion-positive solid tumors.[170-172] In a primary analysis, the efficacy and safety of larotrectinib was reported in 55 patients enrolled in three clinical studies who had locally advanced or metastatic tumors with *NTRK* gene fusions and had progressed on standard chemotherapy received previously.[171] The three clinical trials included a phase 1 dose-finding study in adults, phase 1/2 dose-finding study in the pediatric population, and a phase 2, single-arm, basket trial. The ORR of larotrectinib in these patients was 75% (95% CI, 61%–85%), with 22% complete response and 53% partial response with median duration of response and PFS not reached at the time. In a long-term follow-up analysis, out of 153 patients, 121 patients (79%; 95% CI, 72–85) had objective response with 16% having a complete response, 63% having a partial response, and 12% having stable disease. The median duration of response was 35.2 months (22.8–NE) and the median PFS was 28.3 months.[173] Similarly, entrectinib showed a durable and clinically meaningful response in 54 patients with advanced/metastatic *NTRK* gene fusion tumors enrolled in three phase 1/2 clinical trials with 57.4% ORR, 10.4-month median duration of response, and 11.2-month median PFS.[170] In a long-term efficacy and safety analysis in 121 patients at median follow-up of 25.8 months, 61% reported complete or partial responses, and median duration of response was 20 months (95% CI, 10.1–19.9). Both larotrectinib and entrectinib are FDA-approved for *NTRK* gene fusion solid tumors for patients who have progressed following treatment or have no satisfactory standard therapy. The NCCN Guidelines for Vulvar Cancer recommend larotrectinib and entrectinib as a second-line or subsequent, useful in certain circumstances option for *NTRK* gene fusion-positive tumors and recently changed the category of evidence from category 2B to category 2A.

Gynecologic Survivorship

Treatment for gynecologic cancer typically involves surgery, chemotherapy, hormone therapy, RT, and/or immunotherapy, which may

cause acute, short-term, and long-term toxicities. Surgical approaches may be extensive and cause adhesions to form, which in turn may cause pain and contribute to the development of small bowel obstruction, urinary or gastrointestinal complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a variety of urinary, bowel, and/or sexual effects), and lymphedema.[174,175] Chemotherapy agents vary, though commonly used regimens may pose a significant risk of neurotoxicity, cardiac toxicity, cognitive dysfunction, and the development of hematologic cancers.[176] Long-term estrogen deprivation may cause symptoms such as hot flashes, vaginal dryness, and bone loss. RT may cause long-term complications (eg, fibrosis, stenosis, vulvovaginal atrophy)[177,178] and may predispose patients to subsequent cancers of the skin, subcutaneous tissue, and/or underlying organs that are proximal to the radiation field.[179] Prior pelvic RT may contribute to bone loss and increase the risk of pelvic fractures. Consideration should be given to bone density testing and prophylactic use of bisphosphonates, particularly in patients with osteoporosis. Use of immunotherapy agents in gynecologic cancers is emerging, and to date, long-term effects of these treatments are unknown.[180,181]

Following completion of treatment, all gynecologic cancer survivors should receive regular general medical care that focuses on managing chronic diseases (eg, depression, diabetes, hypertension), monitoring cardiovascular risk factors, receiving recommended vaccinations, and encouraging adoption of a healthy lifestyle (eg, promoting exercise, smoking cessation).[182,183] In order to assess the late and long-term effects of gynecologic cancers, clinicians should comprehensively document the patient's history, including prior treatment history, and conduct a thorough physical examination and provide any necessary imaging and/or laboratory testing.[183] As most treatments for gynecologic cancers will cause sexual dysfunction, early menopause, and infertility, special attention to the resultant medical and psychosocial implications is needed. All patients, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness.[184] Post-radiation use of vaginal dilators and moisturizers is recommended.[177,185] For treatment-related menopause, hormone therapy should be considered. Psychosocial effects may include psychological (eg, depression, anxiety, fear of recurrence, altered body image), financial (eg, return to work, insurance concerns), and interpersonal (eg, relationships, sexuality, intimacy).[183] Patients should be referred to appropriate specialty providers (eg, physical therapy, pelvic floor therapy, sexual therapy, psychotherapy) as needed, based on prior treatment history and assessed risk of developing late effects and/or existing concerns.

Communication and coordination with all clinicians involved in the care of survivors, including primary care clinicians, is critical.[183,186] Providing survivors with a summary of their treatment and recommendations for follow-up is also recommended. To this end, the SGO has developed templates for gynecologic cancer-specific Survivorship Care Plans to aid survivors and their clinicians in summarizing cancer history, treatments received, possible side effects, and recommended follow-up.[187]

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36633525.

2. SEER Cancer Statistics Factsheets: Vulvar Cancer. Bethesda, MD: National Cancer Institute; Available at: http://seer.cancer.gov/statfacts/html/vulva.html. Accessed November 8, 2023.

3. Tergas AI, Tseng JH, Bristow RE. Impact of race and ethnicity on treatment and survival of women with vulvar cancer in the United States. Gynecol Oncol 2013;129:154-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23274562.

4. Chase DM, Lin CC, Craig CD, et al. Disparities in Vulvar Cancer Reported by the National Cancer Database: Influence of Sociodemographic Factors. Obstet Gynecol 2015;126:792-802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26348176.

5. Vulvar Cancer Treatment- for health professionals (PDQ®). Bethesda, MD: 2015. Available at: http://www.cancer.gov/types/vulvar/hp/vulvar-treatment-pdq#section/_1. Accessed November 8, 2023.

6. Stroup AM, Harlan LC, Trimble EL. Demographic, clinical, and treatment trends among women diagnosed with vulvar cancer in the United States. Gynecol Oncol 2008;108:577-583. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18155274.

7. Figge DC. Rare Vulvar Malignancies. In: Greer BE, Berek JS, eds. Current Topics In Obstetrics And Gynecology: Gynecologic Oncology: Treatment Rationale And Techniques.: Elsevier; 1991:239-257.

8. Sideri M, Jones RW, Wilkinson EJ, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. J Reprod Med 2005;50:807-810. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16419625.

9. Bornstein J, Bogliatto F, Haefner HK, et al. The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions. Obstet Gynecol 2016;127:264-268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26942352.

10. Hohn AK, Brambs CE, Hiller GGR, et al. 2020 WHO Classification of Female Genital Tumors. Geburtshilfe Frauenheilkd 2021;81:1145-1153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34629493.

11. Kortekaas KE, Bastiaannet E, van Doorn HC, et al. Vulvar cancer subclassification by HPV and p53 status results in three clinically distinct subtypes. Gynecol Oncol 2020;159:649-656. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32972785.

12. Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer 2008;113:3036-3046. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18980286.

13. Watson M, Saraiya M, Ahmed F, et al. Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods. Cancer 2008;113:2841-2854. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18980203.

14. Gargano JW, Wilkinson EJ, Unger ER, et al. Prevalence of human papillomavirus types in invasive vulvar cancers and vulvar intraepithelial neoplasia 3 in the United States before vaccine introduction. J Low Genit Tract Dis 2012;16:471-479. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22652576.

15. Faber MT, Sand FL, Albieri V, et al. Prevalence and type distribution of human papillomavirus in squamous cell carcinoma and intraepithelial neoplasia of the vulva. Int J Cancer 2017;141:1161-1169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28577297.

16. Li Z, Liu P, Wang Z, et al. Prevalence of human papillomavirus DNA and p16(INK4a) positivity in vulvar cancer and vulvar intraepithelial neoplasia: a systematic review and meta-analysis. Lancet Oncol

2023;24:403-414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36933562.

17. Eifel PJ, Berek JS, Markman MA. Cancer of the cervix, vagina, and vulva. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Principles and Practice of Oncology (ed 9). Philadelphia, PA: Lippincott Williams & Wilkins; 2011:1311-1344.

18. Hampl M, Deckers-Figiel S, Hampl JA, et al. New aspects of vulvar cancer: changes in localization and age of onset. Gynecol Oncol 2008;109:340-345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18407339.

19. Olawaiye AB, Cotler J, Cuello MA, et al. FIGO staging for carcinoma of the vulva: 2021 revision. Int J Gynaecol Obstet 2021;155:43-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34520062.

20. Hacker NF. Revised FIGO staging for carcinoma of the vulva. Int J Gynaecol Obstet 2009;105:105-106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19329116.

21. Li J, Cai Y, Ke G, et al. Validation of the new FIGO staging system (2009) for vulvar cancer in the Chinese population. Gynecol Oncol 2015;137:274-279. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25759305.

22. Tabbaa ZM, Gonzalez J, Sznurkowski JJ, et al. Impact of the new FIGO 2009 staging classification for vulvar cancer on prognosis and stage distribution. Gynecol Oncol 2012;127:147-152. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22704951.

23. Tan J, Chetty N, Kondalsamy-Chennakesavan S, et al. Validation of the FIGO 2009 staging system for carcinoma of the vulva. Int J Gynecol Cancer 2012;22:498-502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22367324.

24. Greer BE, Berek JS. Evolution of the Primary Treatment of Invasive Squamous Cell Carcinoma of the Vulva. In: Greer BE, Berek JS, eds. Current Topics In Obstetrics And Gynecology: Gynecologic Oncology: Treatment Rationale And Techniques: Elsevier; 1991:227-238.

25. Kataoka MY, Sala E, Baldwin P, et al. The accuracy of magnetic resonance imaging in staging of vulvar cancer: a retrospective multi-centre study. Gynecol Oncol 2010;117:82-87. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20092880.

26. Cohn DE, Dehdashti F, Gibb RK, et al. Prospective evaluation of positron emission tomography for the detection of groin node metastases from vulvar cancer. Gynecol Oncol 2002;85:179-184. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11925141.

27. Kamran MW, O'Toole F, Meghen K, et al. Whole-body [18F]fluoro-2-deoxyglucose positron emission tomography scan as combined PET-CT staging prior to planned radical vulvectomy and inguinofemoral lymphadenectomy for squamous vulvar cancer: a correlation with groin node metastasis. Eur J Gynaecol Oncol 2014;35:230-235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24984533.

28. Peiro V, Chiva L, Gonzalez A, et al. [Utility of the PET/CT in vulvar cancer management]. Rev Esp Med Nucl Imagen Mol 2014;33:87-92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24095821.

29. Homesley HD, Bundy BN, Sedlis A, et al. Assessment of current International Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors for survival (a Gynecologic Oncology Group study). Am J Obstet Gynecol 1991;164:997-1003; discussion 1003-1004. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2014852.

30. Burger MP, Hollema H, Emanuels AG, et al. The importance of the groin node status for the survival of T1 and T2 vulval carcinoma patients. Gynecol Oncol 1995;57:327-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7774836.

31. Maggino T, Landoni F, Sartori E, et al. Patterns of recurrence in patients with squamous cell carcinoma of the vulva. A multicenter CTF

Study. Cancer 2000;89:116-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10897008.

32. van der Velden J, van Lindert AC, Lammes FB, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva. The impact on recurrence and survival. Cancer 1995;75:2885-2890. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7773938.

33. Luchini C, Nottegar A, Solmi M, et al. Prognostic implications of extranodal extension in node-positive squamous cell carcinoma of the vulva: A systematic review and meta-analysis. Surg Oncol 2016;25:60-65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26394825.

34. Origoni M, Sideri M, Garsia S, et al. Prognostic value of pathological patterns of lymph node positivity in squamous cell carcinoma of the vulva stage III and IVA FIGO. Gynecol Oncol 1992;45:313-316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1612509.

35. Raspagliesi F, Hanozet F, Ditto A, et al. Clinical and pathological prognostic factors in squamous cell carcinoma of the vulva. Gynecol Oncol 2006;102:333-337. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16466657.

36. Heaps JM, Fu YS, Montz FJ, et al. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol 1990;38:309-314. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2227541.

37. Homesley HD, Bundy BN, Sedlis A, et al. Prognostic factors for groin node metastasis in squamous cell carcinoma of the vulva (a Gynecologic Oncology Group study). Gynecol Oncol 1993;49:279-283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8314530.

38. Aragona AM, Cuneo NA, Soderini AH, Alcoba EB. An analysis of reported independent prognostic factors for survival in squamous cell carcinoma of the vulva: is tumor size significance being underrated? Gynecol Oncol 2014;132:643-648. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24418199.

39. Rouzier R, Haddad B, Plantier F, et al. Local relapse in patients treated for squamous cell vulvar carcinoma: incidence and prognostic value. Obstet Gynecol 2002;100:1159-1167. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12468158.

40. Arvas M, Kahramanoglu I, Bese T, et al. The Role of Pathological Margin Distance and Prognostic Factors After Primary Surgery in Squamous Cell Carcinoma of the Vulva. Int J Gynecol Cancer 2018;28:623-631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29324545.

41. Bogani G, Cromi A, Serati M, et al. Predictors and Patterns of Local, Regional, and Distant Failure in Squamous Cell Carcinoma of the Vulva. Am J Clin Oncol 2017;40:235-240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25503429.

42. Te Grootenhuis NC, Pouwer AW, de Bock GH, et al. Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: A systematic review. Gynecol Oncol 2018;148:622-631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29137809.

43. Figge DC, Tamimi HK, Greer BE. Lymphatic spread in carcinoma of the vulva. Am J Obstet Gynecol 1985;152:387-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4014331.

44. Farias-Eisner R, Cirisano FD, Grouse D, et al. Conservative and individualized surgery for early squamous carcinoma of the vulva: the treatment of choice for stage I and II (T1-2N0-1M0) disease. Gynecol Oncol 1994;53:55-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8175023.

45. Stehman FB, Look KY. Carcinoma of the vulva. Obstet Gynecol 2006;107:719-733. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16507947.

46. Landrum LM, Lanneau GS, Skaggs VJ, et al. Gynecologic Oncology Group risk groups for vulvar carcinoma: improvement in survival in the modern era. Gynecol Oncol 2007;106:521-525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17540438.

47. Kim KW, Shinagare AB, Krajewski KM, et al. Update on imaging of vulvar squamous cell carcinoma. AJR Am J Roentgenol 2013;201:W147-157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23789687.

48. Slomovitz BM, Coleman RL, Oonk MH, et al. Update on sentinel lymph node biopsy for early-stage vulvar cancer. Gynecol Oncol 2015;138:472-477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26022527.

49. Tessier-Cloutier B, Kortekaas KE, Thompson E, et al. Major p53 immunohistochemical patterns in in situ and invasive squamous cell carcinomas of the vulva and correlation with TP53 mutation status. Mod Pathol 2020;33:1595-1605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32203095.

50. Magrina JF, Gonzalez-Bosquet J, Weaver AL, et al. Primary squamous cell cancer of the vulva: radical versus modified radical vulvar surgery. Gynecol Oncol 1998;71:116-121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9784331.

51. Ansink A, van der Velden J. Surgical interventions for early squamous cell carcinoma of the vulva. Cochrane Database Syst Rev 2000;2000:CD002036. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10796849.

52. DeSimone CP, Van Ness JS, Cooper AL, et al. The treatment of lateral T1 and T2 squamous cell carcinomas of the vulva confined to the labium majus or minus. Gynecol Oncol 2007;104:390-395. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17027067.

53. De Hullu JA, Hollema H, Lolkema S, et al. Vulvar carcinoma. The price of less radical surgery. Cancer 2002;95:2331-2338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12436439.

54. Viswanathan AN, Pinto AP, Schultz D, et al. Relationship of margin status and radiation dose to recurrence in post-operative vulvar carcinoma. Gynecol Oncol 2013;130:545-549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23747330.

55. Chan JK, Sugiyama V, Pham H, et al. Margin distance and other clinico-pathologic prognostic factors in vulvar carcinoma: a multivariate analysis. Gynecol Oncol 2007;104:636-641. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17095080.

56. Faul CM, Mirmow D, Huang Q, et al. Adjuvant radiation for vulvar carcinoma: improved local control. Int J Radiat Oncol Biol Phys 1997;38:381-389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9226327.

57. Woelber L, Eulenburg C, Grimm D, et al. The Risk of Contralateral Non-sentinel Metastasis in Patients with Primary Vulvar Cancer and Unilaterally Positive Sentinel Node. Ann Surg Oncol 2016;23:2508-2514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26856721.

58. Coleman RL, Ali S, Levenback CF, et al. Is bilateral lymphadenectomy for midline squamous carcinoma of the vulva always necessary? An analysis from Gynecologic Oncology Group (GOG) 173. Gynecol Oncol 2013;128:155-159. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23201592.

59. Carlson JW, Kauderer J, Hutson A, et al. GOG 244-The lymphedema and gynecologic cancer (LEG) study: Incidence and risk factors in newly diagnosed patients. Gynecol Oncol 2020;156:467-474. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31837831.

60. DiSaia PJ, Creasman WT, Rich WM. An alternate approach to early cancer of the vulva. Am J Obstet Gynecol 1979;133:825-832. Available at: https://www.ncbi.nlm.nih.gov/pubmed/434024.

61. Cacciamani GE, Medina LG, Sayegh AS, et al. Assessment and Reporting of Perioperative Adverse Events and Complications in Patients Undergoing Inguinal Lymphadenectomy for Melanoma, Vulvar Cancer, and Penile Cancer: A Systematic Review and Meta-analysis. World J Surg 2023;47:962-974. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36709215.

62. Van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J Clin

Oncol 2008;26:884-889. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18281661.

63. Levenback CF, Ali S, Coleman RL, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. J Clin Oncol 2012;30:3786-3791. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22753905.

64. Klapdor R, Hillemanns P, Wolber L, et al. Outcome After Sentinel Lymph Node Dissection in Vulvar Cancer: A Subgroup Analysis of the AGO-CaRE-1 Study. Ann Surg Oncol 2017;24:1314-1321. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27896515.

65. Covens A, Vella ET, Kennedy EB, et al. Sentinel lymph node biopsy in vulvar cancer: Systematic review, meta-analysis and guideline recommendations. Gynecol Oncol 2015;137:351-361. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25703673.

66. Oonk MH, van Hemel BM, Hollema H, et al. 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. Lancet Oncol 2010;11:646-652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20537946.

67. Oonk MH, van Os MA, de Bock GH, et al. A comparison of quality of life between vulvar cancer patients after sentinel lymph node procedure only and inguinofemoral lymphadenectomy. Gynecol Oncol 2009;113:301-305. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19297013.

68. Te Grootenhuis NC, van der Zee AG, van Doorn HC, et al. Sentinel nodes in vulvar cancer: Long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I. Gynecol Oncol 2016;140:8-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26428940.

69. Oonk MHM, Slomovitz B, Baldwin PJW, et al. Radiotherapy Versus Inguinofemoral Lymphadenectomy as Treatment for Vulvar Cancer Patients With Micrometastases in the Sentinel Node: Results of GROINSS-V II. J Clin Oncol 2021;39:3623-3632. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34432481.

70. Gien LT, Slomovitz B, Van der Zee A, Oonk M. Phase II activity trial of high-dose radiation and chemosensitization in patients with macrometastatic lymph node spread after sentinel node biopsy in vulvar cancer: GROningen INternational Study on Sentinel nodes in Vulvar cancer III (GROINSS-V III/NRG-GY024). Int J Gynecol Cancer 2023;33:619-622. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36653060.

71. Gonzalez Bosquet J, Magrina JF, Magtibay PM, et al. Patterns of inguinal groin metastases in squamous cell carcinoma of the vulva. Gynecol Oncol 2007;105:742-746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17379281.

72. Hacker NF, Berek JS, Lagasse LD, et al. Individualization of treatment for stage I squamous cell vulvar carcinoma. Obstet Gynecol 1984;63:155-162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6694808.

73. Burke TW, Levenback C, Coleman RL, et al. Surgical therapy of T1 and T2 vulvar carcinoma: further experience with radical wide excision and selective inguinal lymphadenectomy. Gynecol Oncol 1995;57:215-220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7729737.

74. Hacker NF, Van der Velden J. Conservative management of early vulvar cancer. Cancer 1993;71:1673-1677. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8431905.

75. Morgan MA, Mikuta JJ. Surgical management of vulvar cancer. Semin Surg Oncol 1999;17:168-172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10504664.

76. van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. Cochrane Database Syst Rev 2011;2011:CD002224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21563133.

77. Stehman FB, Bundy BN, Thomas G, et al. Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys 1992;24:389-396. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1526880.

78. Hallak S, Ladi L, Sorbe B. Prophylactic inguinal-femoral irradiation as an alternative to primary lymphadenectomy in treatment of vulvar carcinoma. Int J Oncol 2007;31:1077-1085. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17912433.

79. Petereit DG, Mehta MP, Buchler DA, Kinsella TJ. Inguinofemoral radiation of N0,N1 vulvar cancer may be equivalent to lymphadenectomy if proper radiation technique is used. Int J Radiat Oncol Biol Phys 1993;27:963-967. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8244830.

80. Rouzier R, Haddad B, Atallah D, et al. Surgery for vulvar cancer. Clin Obstet Gynecol 2005;48:869-878. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16286833.

81. Magrina JF, Gonzalez-Bosquet J, Weaver AL, et al. Squamous cell carcinoma of the vulva stage IA: long-term results. Gynecol Oncol 2000;76:24-27. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10620436.

82. Yoder BJ, Rufforny I, Massoll NA, Wilkinson EJ. Stage IA vulvar squamous cell carcinoma: an analysis of tumor invasive characteristics and risk. Am J Surg Pathol 2008;32:765-772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18379417.

83. Wilkinson EJ. Superficial invasive carcinoma of the vulva. Clin Obstet Gynecol 1985;28:188-195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3987129.

84. Van der Kolk WL, Van der Zee AGJ, Slomovitz BM, et al. Unilateral inguinofemoral lymphadenectomy in patients with early-stage vulvar squamous cell carcinoma and a unilateral metastatic sentinel lymph node is safe. Gynecol Oncol 2022;167:3-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36085090.

85. Forner DM, Lampe B. Exenteration in the treatment of Stage III/IV vulvar cancer. Gynecol Oncol 2012;124:87-91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21992967.

86. Miller B, Morris M, Levenback C, et al. Pelvic exenteration for primary and recurrent vulvar cancer. Gynecol Oncol 1995;58:202-205. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7622106.

87. Hoffman MS, Cavanagh D, Roberts WS, et al. Ultraradical surgery for advanced carcinoma of the vulva: an update. Int J Gynecol Cancer 1993;3:369-372. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11578371.

88. Gadducci A, Cionini L, Romanini A, et al. Old and new perspectives in the management of high-risk, locally advanced or recurrent, and metastatic vulvar cancer. Crit Rev Oncol Hematol 2006;60:227-241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16945551.

89. Boronow RC. Combined therapy as an alternative to exenteration for locally advanced vulvo-vaginal cancer: rationale and results. Cancer 1982;49:1085-1091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7059935.

90. Fuh KC, Berek JS. Current management of vulvar cancer. Hematol Oncol Clin North Am 2012;26:45-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22244661.

91. Leiserowitz GS, Russell AH, Kinney WK, et al. Prophylactic chemoradiation of inguinofemoral lymph nodes in patients with locally extensive vulvar cancer. Gynecol Oncol 1997;66:509-514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9299268.

92. Russell AH, Mesic JB, Scudder SA, et al. Synchronous radiation and cytotoxic chemotherapy for locally advanced or recurrent squamous cancer of the vulva. Gynecol Oncol 1992;47:14-20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1427394.

93. Thomas G, Dembo A, DePetrillo A, et al. Concurrent radiation and chemotherapy in vulvar carcinoma. Gynecol Oncol 1989;34:263-267. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2504651.

94. Eifel PJ, Morris M, Burke TW, et al. Prolonged continuous infusion cisplatin and 5-fluorouracil with radiation for locally advanced carcinoma of the vulva. Gynecol Oncol 1995;59:51-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7557615.

95. Lupi G, Raspagliesi F, Zucali R, et al. Combined preoperative chemoradiotherapy followed by radical surgery in locally advanced vulvar carcinoma. A pilot study. Cancer 1996;77:1472-1478. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8608531.

96. Moore DH, Thomas GM, Montana GS, et al. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. Int J Radiat Oncol Biol Phys 1998;42:79-85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9747823.

97. Geisler JP, Manahan KJ, Buller RE. Neoadjuvant chemotherapy in vulvar cancer: avoiding primary exenteration. Gynecol Oncol 2006;100:53-57. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16257042.

98. Landoni F, Maneo A, Zanetta G, et al. Concurrent preoperative chemotherapy with 5-fluorouracil and mitomycin C and radiotherapy (FUMIR) followed by limited surgery in locally advanced and recurrent vulvar carcinoma. Gynecol Oncol 1996;61:321-327. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8641609.

99. Berek JS, Heaps JM, Fu YS, et al. Concurrent cisplatin and 5-fluorouracil chemotherapy and radiation therapy for advanced-stage squamous carcinoma of the vulva. Gynecol Oncol 1991;42:197-201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1955180.

100. Koh WJ, Wallace HJ, 3rd, Greer BE, et al. Combined radiotherapy and chemotherapy in the management of local-regionally advanced vulvar cancer. Int J Radiat Oncol Biol Phys 1993;26:809-816. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8344850.

101. Cunningham MJ, Goyer RP, Gibbons SK, et al. Primary radiation, cisplatin, and 5-fluorouracil for advanced squamous carcinoma of the vulva. Gynecol Oncol 1997;66:258-261. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9264573.

102. Gerszten K, Selvaraj RN, Kelley J, Faul C. Preoperative chemoradiation for locally advanced carcinoma of the vulva. Gynecol Oncol 2005;99:640-644. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16169579.

103. Tans L, Ansink AC, van Rooij PH, et al. The role of chemo-radiotherapy in the management of locally advanced carcinoma of the vulva: single institutional experience and review of literature. Am J Clin Oncol 2011;34:22-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20087157.

104. Han SC, Kim DH, Higgins SA, et al. Chemoradiation as primary or adjuvant treatment for locally advanced carcinoma of the vulva. Int J Radiat Oncol Biol Phys 2000;47:1235-1244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10889377.

105. Rao YJ, Chin RI, Hui C, et al. Improved survival with definitive chemoradiation compared to definitive radiation alone in squamous cell carcinoma of the vulva: A review of the National Cancer Database. Gynecol Oncol 2017;146:572-579. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28662775.

106. Montana GS, Thomas GM, Moore DH, et al. Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study. Int J Radiat Oncol Biol Phys 2000;48:1007-1013. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11072157.

107. Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. Gynecol Oncol 2012;124:529-533. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22079361.

108. van Triest B, Rasing M, van der Velden J, et al. Phase II study of definitive chemoradiation for locally advanced squamous cell cancer of the vulva: An efficacy study. Gynecol Oncol 2021;163:117-124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34301412.

109. Natesan D, Hong JC, Foote J, et al. Primary Versus Preoperative Radiation for Locally Advanced Vulvar Cancer. Int J Gynecol Cancer 2017;27:794-804. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28333840.

110. Shylasree TS, Bryant A, Howells RE. Chemoradiation for advanced primary vulval cancer. Cochrane Database Syst Rev 2011;2011:CD003752. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21491387.

111. van Doorn HC, Ansink A, Verhaar-Langereis M, Stalpers L. Neoadjuvant chemoradiation for advanced primary vulvar cancer. Cochrane Database Syst Rev 2006:CD003752. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16856018.

112. Reade CJ, Eiriksson LR, Mackay H. Systemic therapy in squamous cell carcinoma of the vulva: current status and future directions. Gynecol Oncol 2014;132:780-789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24296343.

113. Candelaria M, Garcia-Arias A, Cetina L, Duenas-Gonzalez A. Radiosensitizers in cervical cancer. Cisplatin and beyond. Radiat Oncol 2006;1:15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16722549.

114. Lorvidhaya V, Chitapanarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. Int J Radiat Oncol Biol Phys 2003;55:1226-1232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12654431.

115. Cerrotta A, Gardan G, Cavina R, et al. Concurrent radiotherapy and weekly paclitaxel for locally advanced or recurrent squamous cell carcinoma of the uterine cervix. A pilot study with intensification of dose. Eur J Gynaecol Oncol 2002;23:115-119. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12013105.

116. Pattaranutaporn P, Thirapakawong C, Chansilpa Y, et al. Phase II study of concurrent gemcitabine and radiotherapy in locally advanced stage IIIB cervical carcinoma. Gynecol Oncol 2001;81:404-407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11371129.

117. Han SN, Vergote I, Amant F. Weekly paclitaxel/carboplatin in the treatment of locally advanced, recurrent, or metastatic vulvar cancer. Int J Gynecol Cancer 2012;22:865-868. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22552830.

118. Witteveen PO, van der Velden J, Vergote I, et al. Phase II study on paclitaxel in patients with recurrent, metastatic or locally advanced vulvar cancer not amenable to surgery or radiotherapy: a study of the EORTC-GCG (European Organisation for Research and Treatment of Cancer--Gynaecological Cancer Group). Ann Oncol 2009;20:1511-1516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19487487.

119. Horowitz NS, Olawaiye AB, Borger DR, et al. Phase II trial of erlotinib in women with squamous cell carcinoma of the vulva. Gynecol Oncol 2012;127:141-146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22750258.

120. Jolly S, Soni P, Gaffney DK, et al. ACR Appropriateness Criteria(R) Adjuvant Therapy in Vulvar Cancer. Oncology (Williston Park) 2015;29:867-872, 874-865. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26568534.

121. Homesley HD, Bundy BN, Sedlis A, Adcock L. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. Obstet Gynecol 1986;68:733-740. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3785783.

122. Kunos C, Simpkins F, Gibbons H, et al. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. Obstet Gynecol 2009;114:537-546. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19701032.

123. Swanick CW, Eifel PJ, Huo J, et al. Challenges to delivery and effectiveness of adjuvant radiation therapy in elderly patients with node-positive vulvar cancer. Gynecol Oncol 2017;146:87-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28506563.

124. Fons G, Groenen SM, Oonk MH, et al. Adjuvant radiotherapy in patients with vulvar cancer and one intra capsular lymph node metastasis is not beneficial. Gynecol Oncol 2009;114:343-345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19481242.

125. Mahner S, Jueckstock J, Hilpert F, et al. Adjuvant therapy in lymph node-positive vulvar cancer: the AGO-CaRE-1 study. J Natl Cancer Inst 2015;107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25618900.

126. Parthasarathy A, Cheung MK, Osann K, et al. The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. Gynecol Oncol 2006;103:1095-1099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16889821.

127. Woelber L, Eulenburg C, Choschzick M, et al. Prognostic role of lymph node metastases in vulvar cancer and implications for adjuvant treatment. Int J Gynecol Cancer 2012;22:503-508. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22266935.

128. Gill BS, Bernard ME, Lin JF, et al. Impact of adjuvant chemotherapy with radiation for node-positive vulvar cancer: A National Cancer Data Base (NCDB) analysis. Gynecol Oncol 2015;137:365-372. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25868965.

129. Swanick CW, Smith GL, Huo J, et al. (P021) Delivery and Outcomes of Adjuvant Radiation Therapy in Older Women With Node-Positive Vulvar Cancer. Oncology (Williston Park) 2016;30 Suppl. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27083660.

130. Ignatov T, Eggemann H, Burger E, et al. Adjuvant radiotherapy for vulvar cancer with close or positive surgical margins. J Cancer Res Clin Oncol 2016;142:489-495. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26498775.

131. van Beekhuizen HJ, Auzin M, van den Einden LC, et al. Lymph node count at inguinofemoral lymphadenectomy and groin recurrences in vulvar cancer. Int J Gynecol Cancer 2014;24:773-778. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24662136.

132. Bell JG, Lea JS, Reid GC. Complete groin lymphadenectomy with preservation of the fascia lata in the treatment of vulvar carcinoma. Gynecol Oncol 2000;77:314-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10785485.

133. Stehman FB, Bundy BN, Dvoretsky PM, Creasman WT. Early stage I carcinoma of the vulva treated with ipsilateral superficial inguinal lymphadenectomy and modified radical hemivulvectomy: a prospective study of the Gynecologic Oncology Group. Obstet Gynecol 1992;79:490-497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1553164.

134. Kirby TO, Rocconi RP, Numnum TM, et al. Outcomes of Stage I/II vulvar cancer patients after negative superficial inguinal lymphadenectomy. Gynecol Oncol 2005;98:309-312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15975642.

135. Gonzalez Bosquet J, Magrina JF, Gaffey TA, et al. Long-term survival and disease recurrence in patients with primary squamous cell carcinoma of the vulva. Gynecol Oncol 2005;97:828-833. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15896831.

136. Nooij LS, Brand FA, Gaarenstroom KN, et al. Risk factors and treatment for recurrent vulvar squamous cell carcinoma. Crit Rev Oncol Hematol 2016;106:1-13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27637349.

137. Gien LT, Sutradhar R, Thomas G, et al. Patient, tumor, and health system factors affecting groin node dissection rates in vulvar carcinoma: A population-based cohort study. Gynecol Oncol 2015;139:465-470. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26483007.

138. Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO)

recommendations. Gynecol Oncol 2017;146:3-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28372871.

139. Mahner S, Prieske K, Grimm D, et al. Systemic treatment of vulvar cancer. Expert Rev Anticancer Ther 2015;15:629-637. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25997120.

140. Salom EM, Penalver M. Recurrent vulvar cancer. Curr Treat Options Oncol 2002;3:143-153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12057077.

141. Piura B, Masotina A, Murdoch J, et al. Recurrent squamous cell carcinoma of the vulva: a study of 73 cases. Gynecol Oncol 1993;48:189-195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8428690.

142. Raffetto N, Tombolini V, Santarelli M, et al. Radiotherapy alone and chemoirradiation in recurrent squamous cell carcinoma of the vulva. Anticancer Res 2003;23:3105-3108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12926170.

143. Podratz KC, Symmonds RE, Taylor WF, Williams TJ. Carcinoma of the vulva: analysis of treatment and survival. Obstet Gynecol 1983;61:63-74. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6823350.

144. Chiantera V, Rossi M, De Iaco P, et al. Morbidity after pelvic exenteration for gynecological malignancies: a retrospective multicentric study of 230 patients. Int J Gynecol Cancer 2014;24:156-164. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24362721.

145. Stehman FB, Bundy BN, Ball H, Clarke-Pearson DL. Sites of failure and times to failure in carcinoma of the vulva treated conservatively: a Gynecologic Oncology Group study. Am J Obstet Gynecol 1996;174:1128-1132; discussion 1132-1123. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8623839.

146. Hopkins MP, Reid GC, Morley GW. The surgical management of recurrent squamous cell carcinoma of the vulva. Obstet Gynecol 1990;75:1001-1005. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2342725.

147. Bellati F, Angioli R, Manci N, et al. Single agent cisplatin chemotherapy in surgically resected vulvar cancer patients with multiple inguinal lymph node metastases. Gynecol Oncol 2005;96:227-231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15589606.

148. Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet 2017;390:1654-1663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28756902.

149. Rosen VM, Guerra I, McCormack M, et al. Systematic Review and Network Meta-Analysis of Bevacizumab Plus First-Line Topotecan-Paclitaxel or Cisplatin-Paclitaxel Versus Non-Bevacizumab-Containing Therapies in Persistent, Recurrent, or Metastatic Cervical Cancer. Int J Gynecol Cancer 2017;27:1237-1246. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28448304.

150. Kitagawa R, Katsumata N, Shibata T, et al. Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505. J Clin Oncol 2015;33:2129-2135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25732161.

151. Lorusso D, Petrelli F, Coinu A, et al. A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer. Gynecol Oncol 2014;133:117-123. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24486604.

152. Santeufemia DA, Capobianco G, Re GL, et al. Cisplatin-gemcitabine as palliative chemotherapy in advanced squamous vulvar carcinoma: report of two cases. Eur J Gynaecol Oncol 2012;33:421-422. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23091903.

153. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or

persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2009;27:4649-4655. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19720909.

154. Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med 2018;379:341-351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29863979.

155. Tewari KS, Monk BJ, Vergote I, et al. Survival with Cemiplimab in Recurrent Cervical Cancer. N Engl J Med 2022;386:544-555. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35139273.

156. Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin Oncol 2016;39:98-106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26558876.

157. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580-6587. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23087408.

158. Wherry EJ. T cell exhaustion. Nat Immunol 2011;12:492-499. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21739672.

159. Hecking T, Thiesler T, Schiller C, et al. Tumoral PD-L1 expression defines a subgroup of poor-prognosis vulvar carcinomas with non-viral etiology. Oncotarget 2017;8:92890-92903. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29190964.

160. Howitt BE, Sun HH, Roemer MG, et al. Genetic Basis for PD-L1 Expression in Squamous Cell Carcinomas of the Cervix and Vulva. JAMA Oncol 2016;2:518-522. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26913631.

161. Naing A, Meric-Bernstam F, Stephen B, et al. Phase 2 study of pembrolizumab in patients with advanced rare cancers. J Immunother Cancer 2020;8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32188704.

162. How JA, Jazaeri AA, Soliman PT, et al. Pembrolizumab in vaginal and vulvar squamous cell carcinoma: a case series from a phase II basket trial. Sci Rep 2021;11:3667. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33574401.

163. Chung HC, Ros W, Delord JP, et al. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2019;37:1470-1478. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30943124.

164. Shapira-Frommer R, Mileshkin L, Manzyuk L, et al. Efficacy and safety of pembrolizumab for patients with previously treated advanced vulvar squamous cell carcinoma: Results from the phase 2 KEYNOTE-158 study. Gynecol Oncol 2022;166:211-218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35361487.

165. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353-1365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32919526.

166. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2020;38:1-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31682550.

167. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. 2017. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication. Accessed November 8, 2023.

168. FDA approves pembrolizumab for adults and children with TMB-H solid tumors. 2020. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors. Accessed November 8, 2023.

169. Naumann RW, Hollebecque A, Meyer T, et al. Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results From the Phase I/II CheckMate 358 Trial. J Clin Oncol 2019;37:2825-2834. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31487218.

170. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31838007.

171. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med 2018;378:731-739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29466156.

172. Hong DS, Bauer TM, Lee JJ, et al. Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study. Ann Oncol 2019;30:325-331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30624546.

173. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020;21:531-540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105622.

174. Dessources K, Aviki E, Leitao MM, Jr. Lower extremity lymphedema in patients with gynecologic malignancies. Int J Gynecol Cancer 2020;30:252-260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31915136.

175. Bona AF, Ferreira KR, Carvalho RBM, et al. Incidence, prevalence, and factors associated with lymphedema after treatment for cervical cancer: a systematic review. Int J Gynecol Cancer 2020;30:1697-1704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32863276.

176. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. J Clin Oncol 2020;38:3325-3348. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32663120.

177. Stahl JM, Qian JM, Tien CJ, et al. Extended duration of dilator use beyond 1 year may reduce vaginal stenosis after intravaginal high-dose-rate brachytherapy. Support Care Cancer 2019;27:1425-1433. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30187220.

178. Park HS, Ratner ES, Lucarelli L, et al. Predictors of vaginal stenosis after intravaginal high-dose-rate brachytherapy for endometrial carcinoma. Brachytherapy 2015;14:464-470. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25887343.

179. Dracham CB, Shankar A, Madan R. Radiation induced secondary malignancies: a review article. Radiat Oncol J 2018;36:85-94. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29983028.

180. Borella F, Preti M, Bertero L, et al. Is There a Place for Immune Checkpoint Inhibitors in Vulvar Neoplasms? A State of the Art Review. Int J Mol Sci 2020;22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33375467.

181. Schepisi G, Casadei C, Toma I, et al. Immunotherapy and Its Development for Gynecological (Ovarian, Endometrial and Cervical) Tumors: From Immune Checkpoint Inhibitors to Chimeric Antigen Receptor (CAR)-T Cell Therapy. Cancers (Basel) 2021;13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33671294.

182. Lin KY, Frawley HC, Denehy L, et al. Exercise interventions for patients with gynaecological cancer: a systematic review and meta-analysis. Physiotherapy 2016;102:309-319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27553642.

183. Nekhlyudov L, Mollica MA, Jacobsen PB, et al. Developing a Quality of Cancer Survivorship Care Framework: Implications for Clinical Care, Research, and Policy. J Natl Cancer Inst 2019;111:1120-1130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31095326.

184. Bober SL, Reese JB, Barbera L, et al. How to ask and what to do: a guide for clinical inquiry and intervention regarding female sexual health after cancer. Current Opinion in Supportive and Palliative Care 2016;10. Available at: https://journals.lww.com/co-supportiveandpalliativecare/Fulltext/2016/03000/How_to_ask_and_what_to_do__a_guide_for_clinical.12.aspx.

185. Damast S, Jeffery DD, Son CH, et al. Literature Review of Vaginal Stenosis and Dilator Use in Radiation Oncology. Pract Radiat Oncol 2019;9:479-491. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31302301.

186. Campbell G, Thomas TH, Hand L, et al. Caring for Survivors of Gynecologic Cancer: Assessment and Management of Long-term and Late Effects. Semin Oncol Nurs 2019;35:192-201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30867102.

187. SGO/FWC Survivorship Toolkit. Available at: https://www.sgo.org/resources/survivorship-toolkit/. Accessed November 8, 2023.