National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Vulvar Cancer (Squamous Cell Carcinoma)

Version 2.2019 — December 17, 2018

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/clinicians.aspx.

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

For vulvar melanoma see the NCCN Guidelines for Cutaneous Melanoma

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Updates in Version 2.2019 of the NCCN Guidelines for Vulvar Cancer from Version 1.2019 include:

VULVA-A Principles of Pathology
- **This is a new section that includes recommendations for pathologic assessment after vulvectomy.**

MS-1
- **The Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 1.2019 of the NCCN Guidelines for Vulvar Cancer from Version 1.2018 include:

VULVA-1
- **Workup: New bullet added, "*For elderly patients with vulvar cancer, see the NCCN Guidelines for Older Adult Oncology*"**

VULVA-3
- **Footnote k revised: "Other primary risk factors include: *close tumor margins*, lymphovascular invasion, ~~negative but close tumor margins (<8 mm)~~, tumor size...."**

VULVA-4
- **Adjuvant therapy to the nodes: For SLN(s) positive, recommendation revised, "EBRT ± concurrent chemotherapy ~~(category 1 for radiation)~~."**
- **Footnote l revised: "If ipsilateral groin is positive, 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 primary tumor diameter ≤2 cm and depth of invasion ≤5 mm and with a clinically negative contralateral groin examination, a contralateral groin dissection or radiation may be omitted. (Bosquet JG, Magrina Jf, Magtibay PM, et al. Patterns of inguinal groin metastases in squamous cell carcinoma of the vulva. Gynecologic Oncol 2007;105:742-746.)*"**

VULVA-5
- **Footnote o revised: "Larger T2 tumors: >4 cm *and/*or ~~with~~ involvement of the urethra, vagina, or anus."**

VULVA-6
- **Additional Treatment: Revised, "Consider biopsy of tumor bed to confirm pathologic~~ally~~ complete response (*p*CR)."**

VULVA-8
- **Workup: Second bullet revised, "Consider biopsy to confirm *local and/or* distant ~~metastasis~~ *recurrence.*"**
- **The following reference was removed as footnote: "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 Gynecol Oncology (SGO) recommendations. Gynecol Oncol 2017;146:3-10." It is included in the Discussion section.**

VULVA-9
- **Therapy for Recurrence: Recommendation revised, "Radical excision ~~and~~ ± unilateral or bilateral inguinofemoral LN dissection ~~(if lymphadenectomy not previously performed)~~"**

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VULVA-B Principles of Surgery
- 1 of 4 Tumor Margin Status
  - Third bullet revised: "In the setting of a close or positive surgical tumor margin ~~(<8 mm from tumor)~~, re-resection may be considered to obtain ~~more adequate~~ *wider* margins."
  - Footnote removed: "For margins that are free but close (>0 mm but <8 mm), evidence is lacking to support decreased recurrence and improved survival with re-resection of disease or adjuvant local radiation to the primary tumor site."
- 2 of 4 Surgical Staging
  - New bullet added: "*Lymphadenectomy or SLN evaluation can be omitted in patients with stage IA primary disease with clinically negative groins due to a <1% risk of lymphatic metastases*."
  - Bullet removed: "Some patients are not candidates for lymphadenectomy including those with stage IA disease due to a <1% risk of lymphatic metastases."
- 3 of 4 Inguinofemoral Senitnel Lymph Node Biopsy
  - Seventh bullet revised: "...Approximately 3–4 cc of dye is injected *peritumorally* using a four-point injection technique at 2, 5, 7, and 10 o'clock...

VULVA-C Principles of Radiation Therapy
- This section was extensively revised.

VULVA-D Systemic Therapy
- The NCCN Categories of Preference has been applied to all of the suggested regimens.
- Chemotherapy for Advanced, Recurrent/Metastatic Disease
  - "*Cisplatin/paclitaxel/bevacizumab"* added as an option
  - "*Carboplatin/paclitaxel/bevacizumab*" added as a category 2B recommendation.
  - "Pembrolizumab for MSI-H/dMMR tumors" changed to "Pembrolizumab for *PD-L1-positive or* MSI-H/dMMR tumors". A corresponding footnote regarding pembrolizumab for PD-L1–positive tumors was also added, "*Recommended for disease progression on or after chemotherapy in patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test*."

SQUAMOUS CELL CARCINOMA[a]

WORKUP

- H&P
- CBC
- Biopsy, pathologic review[b]
- LFT/renal function studies
- Imaging[c] as needed for delineating extent of tumor or for treatment planning
- EUA cystoscopy or proctoscopy as indicated
- Smoking cessation and counseling intervention if indicated (See NCCN Guidelines for Smoking Cessation)
- Consider HPV testing
- Consider HIV testing[d]
- For elderly patients with vulvar cancer, see the NCCN Guidelines for Older Adult Oncology

CLINICAL STAGE[b]

PRIMARY TREATMENT

CLINICAL STAGE[b]	PRIMARY TREATMENT
Early stage (T1, smaller T2[e])	See Primary Treatment (VULVA-2)
Locally advanced (Larger T2, T3: non-visceral–sparing primary surgery)	See Primary Treatment (VULVA-5)
Metastatic disease beyond pelvis (Any T, any N, M1 beyond pelvis)	See Primary Treatment (VULVA-7)

[a]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.
[b]See Principles of Pathology (VULVA-A).
[c]See Principles of Imaging (VULVA-B).
[d]Consider HIV testing, especially in younger patients. 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.
[e]Smaller T2 tumors: ≤4 cm.

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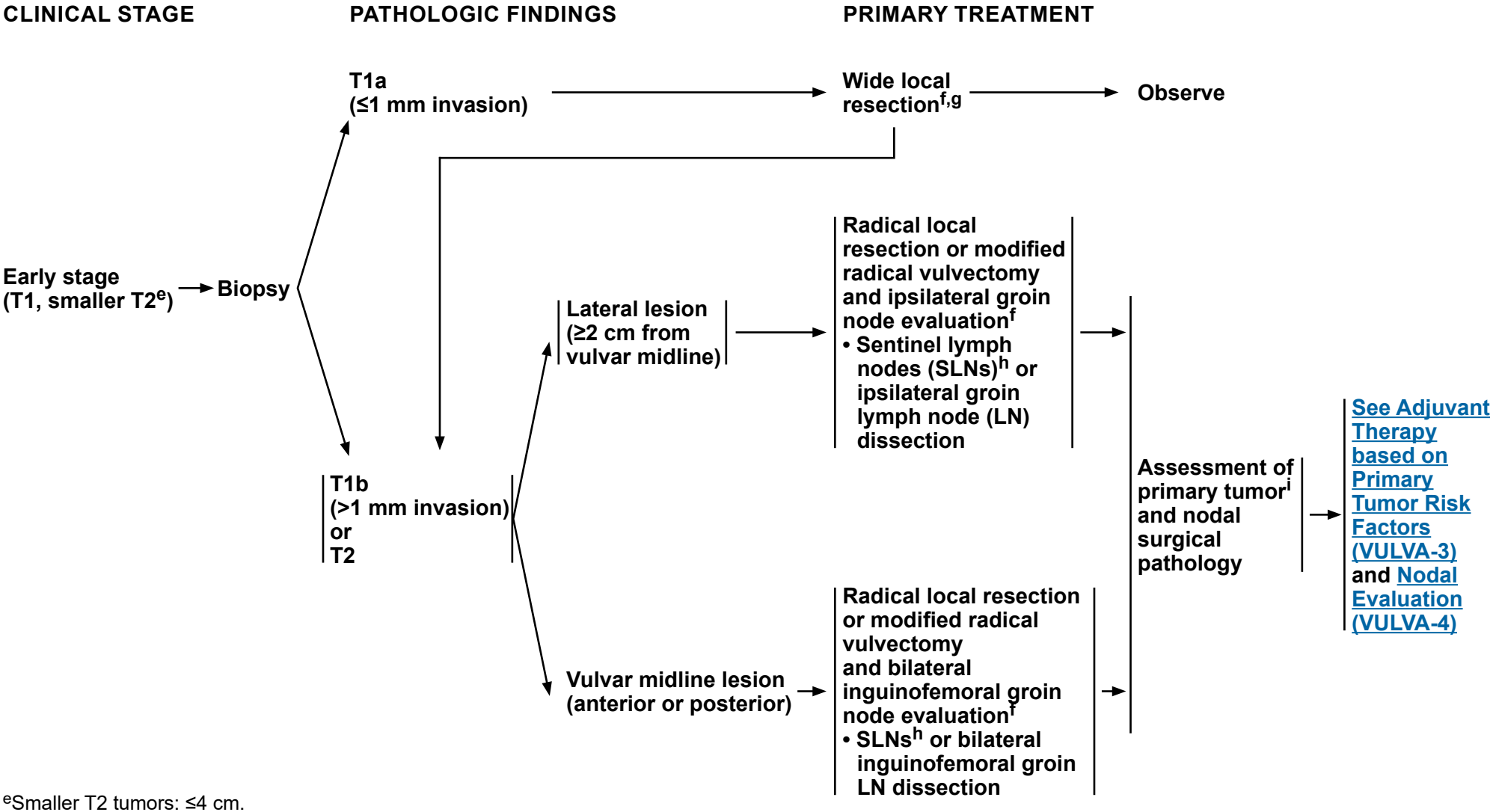

[e]Smaller T2 tumors: ≤4 cm.
[f]See Principles of Surgery (VULVA-C).
[g]If wide local resection pathology reveals tumor in aggregate of ≥1 mm invasion, then additional surgery may be warranted.
[h]Groin node dissection is required on side(s) where sentinel nodes are not detected.
[i]See Principles of Surgery: Tumor Margin Status (VULVA-C 1 of 4).

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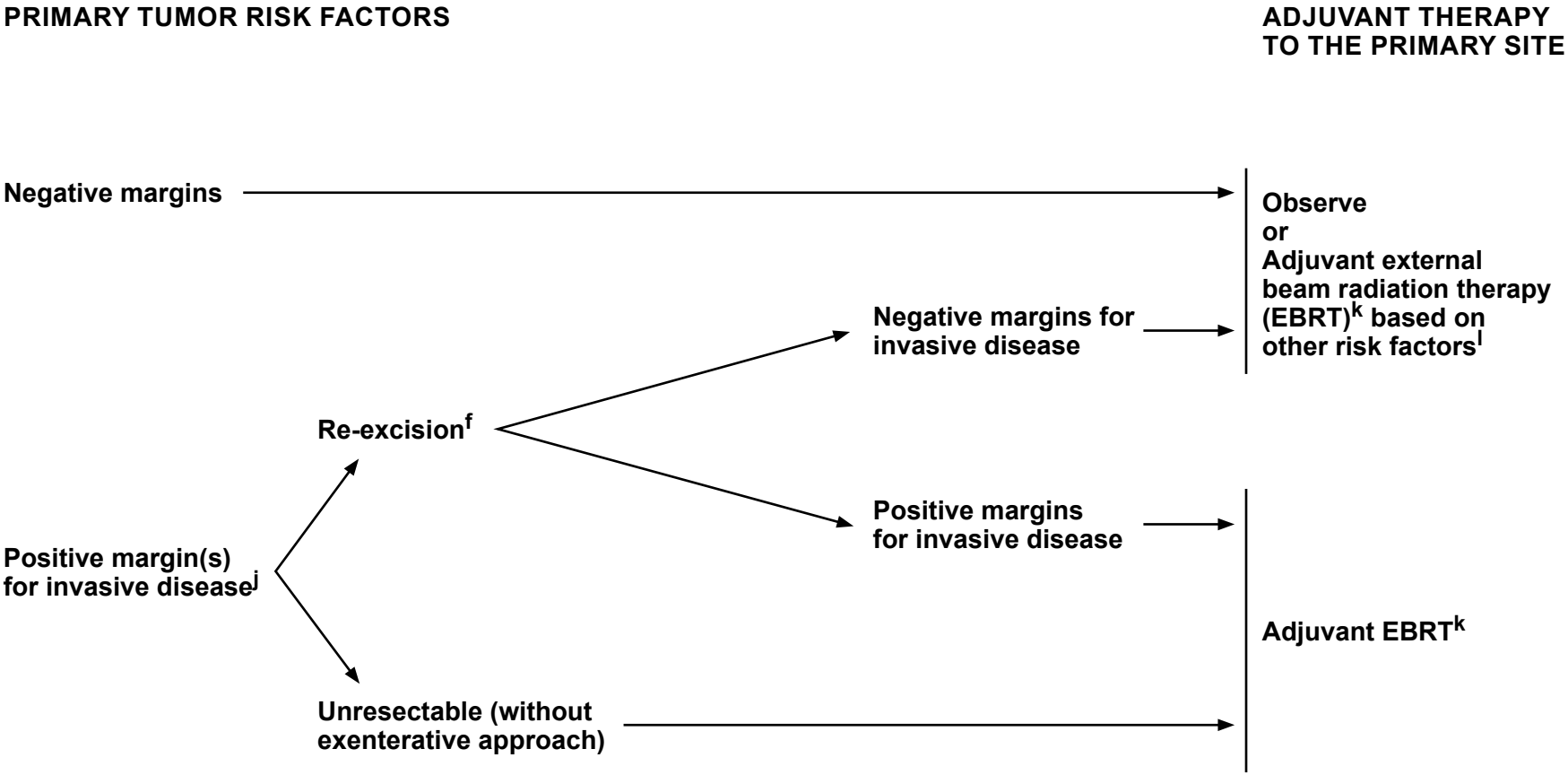

See Surveillance (VULVA-8)

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

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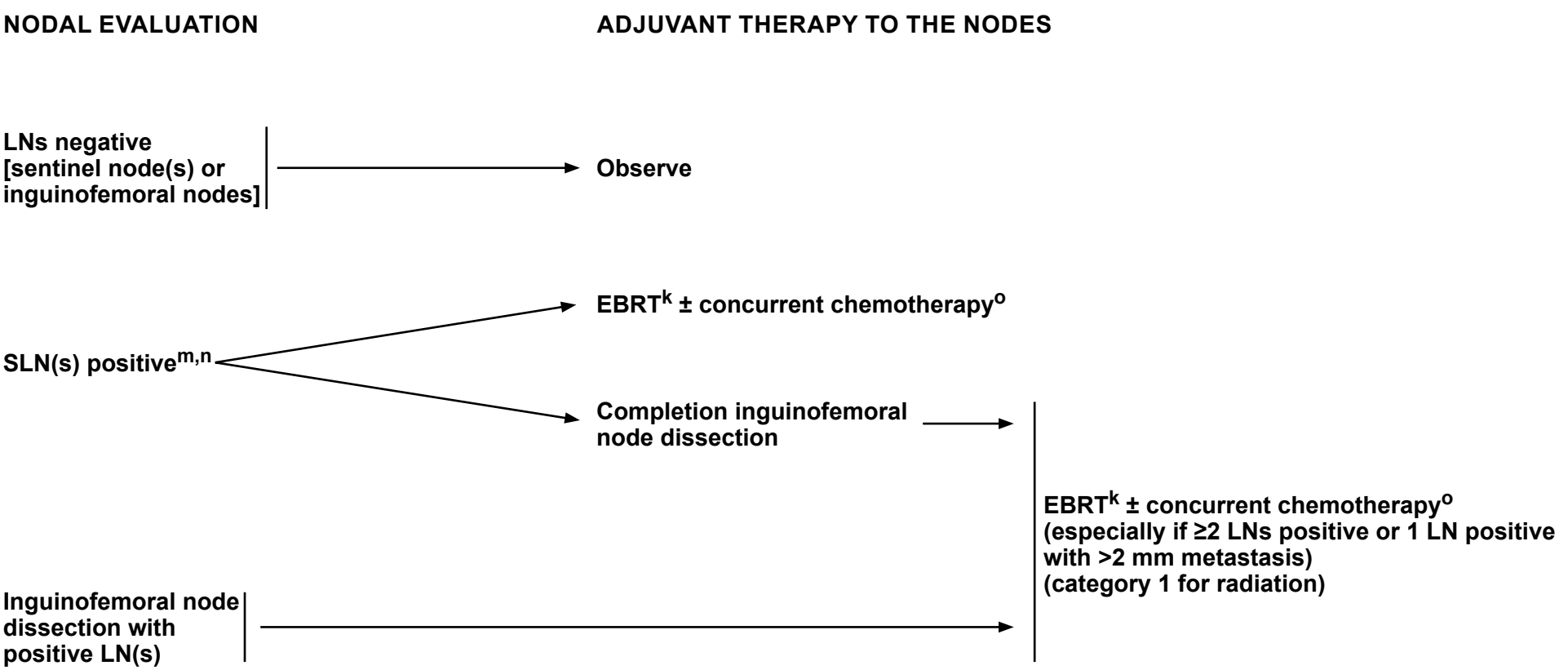

[k] See Principles of Radiation Therapy (VULVA-D).

[m] If ipsilateral groin is positive, 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 primary tumor diameter ≤2 cm and depth of invasion ≤5 mm and with a clinically negative contralateral groin examination, a contralateral groin dissection or radiation may be omitted. (Bosquet JG, Magrina Jf, Magtibay PM, et al. Patterns of inguinal groin metastases in squamous cell carcinoma of the vulva. Gynecologic Oncol 2007;105:742-746.)

[n] See Principles of Surgery: Inguinofemoral Sentinel Lymph Node Biopsy (VULVA-C 3 of 4).

[o] See Systemic Therapy (VULVA-E).

See Surveillance (VULVA-8)

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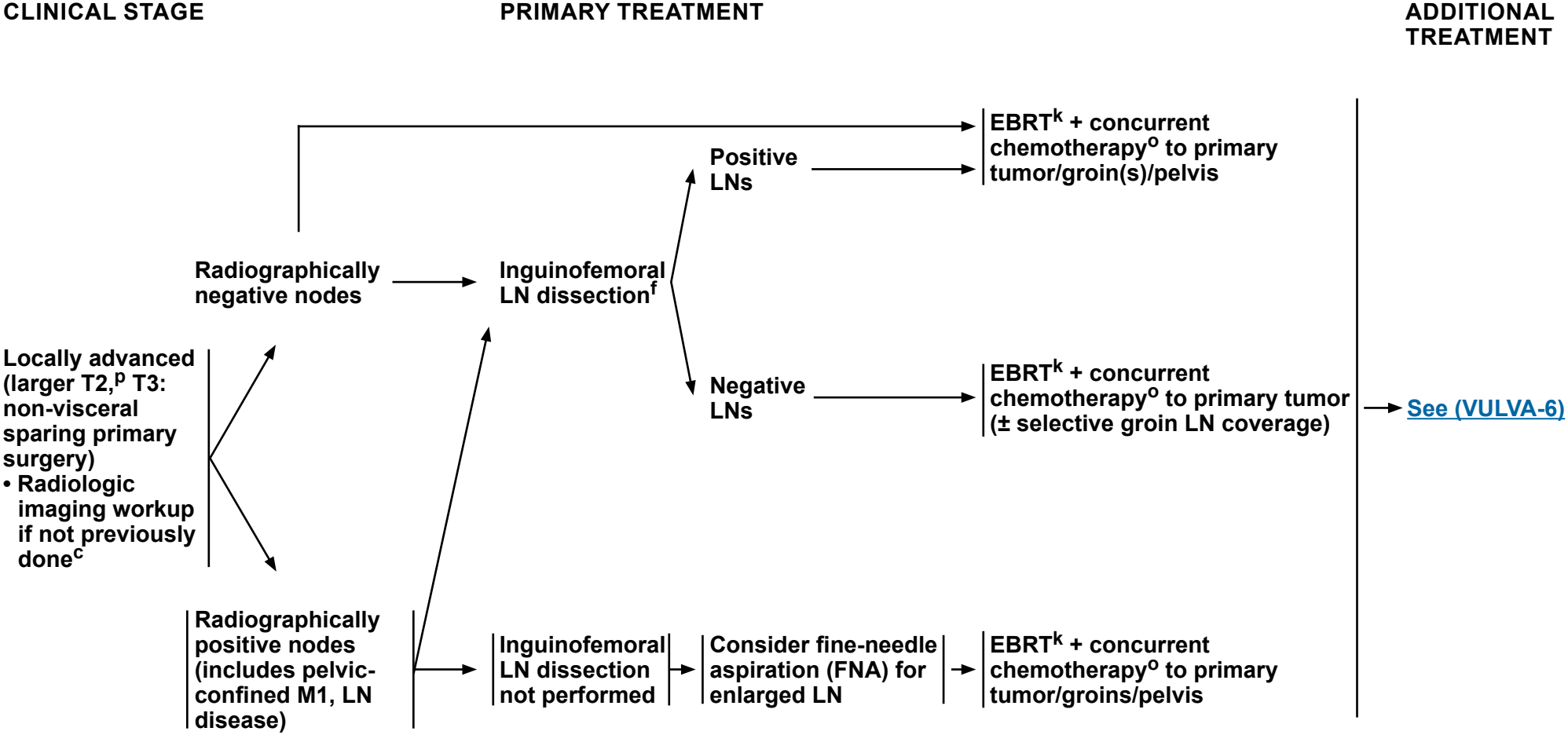

[c] See Principles of Imaging (VULVA-B).
[f] See Principles of Surgery (VULVA-C).
[k] See Principles of Radiation Therapy (VULVA-D).
[o] See Systemic Therapy (VULVA-E).
[p] Larger T2 tumors: >4 cm and/or involvement of the urethra, vagina, or anus.

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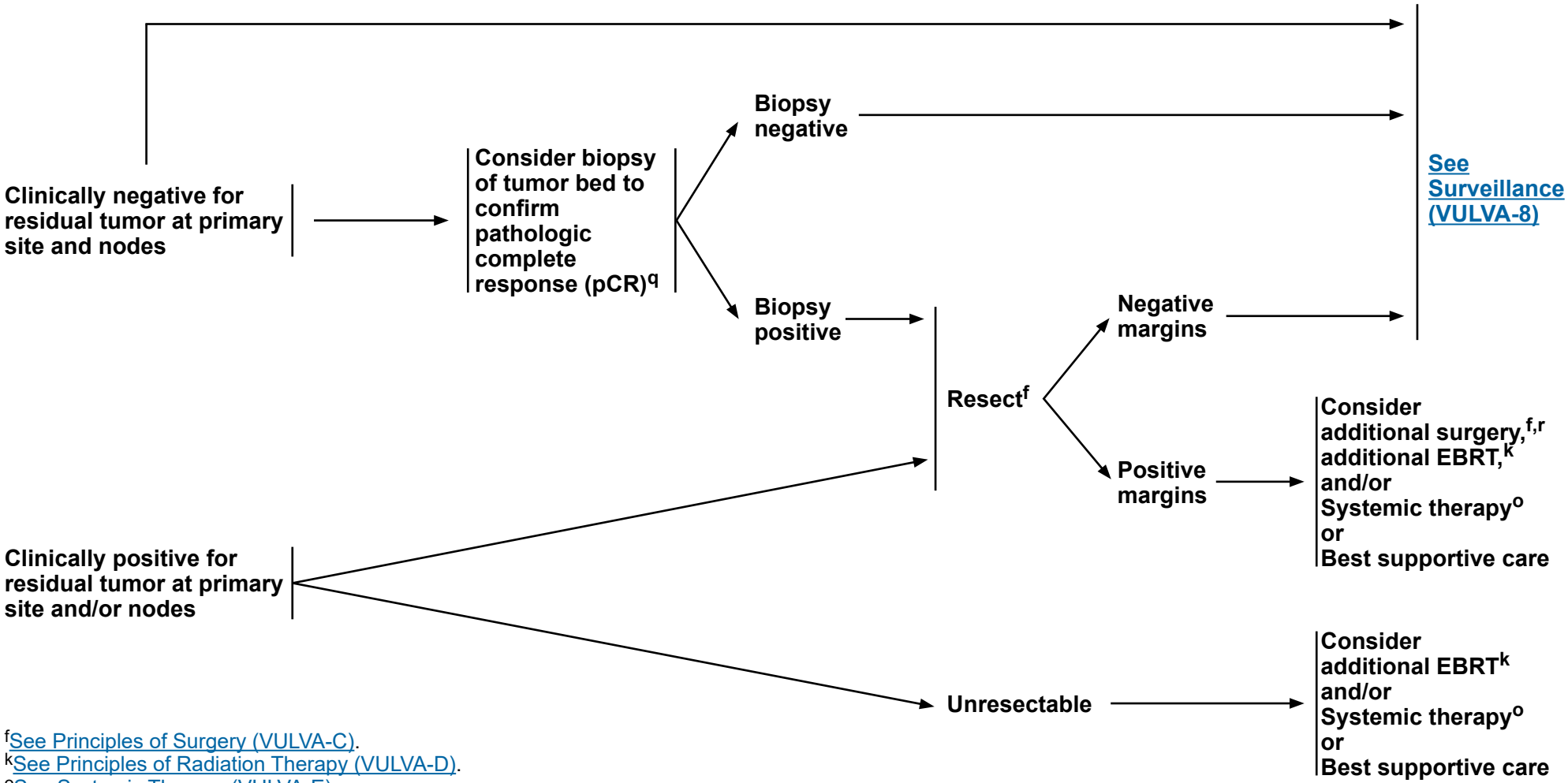
EVALUATION OF RESPONSE TO EBRT + CONCURRENT CHEMOTHERAPY

ADDITIONAL TREATMENT



[f] See Principles of Surgery (VULVA-C).
[k] See Principles of Radiation Therapy (VULVA-D).
[o] See Systemic Therapy (VULVA-E).
[q] No sooner than 3 months from completion of treatment.
[r] Consider pelvic exenteration for select cases with a central recurrence.

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CLINICAL STAGE	PRIMARY TREATMENT
Metastatic disease beyond pelvis (any T, any N, M1 beyond pelvis)	**EBRT[k] for locoregional control/symptom palliation and/or Systemic therapy[o] or Best supportive care (See NCCN Guidelines for Palliative Care)**

[k] See Principles of Radiation Therapy (VULVA-D).
[o] See Systemic Therapy (VULVA-E).

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SURVEILLANCE

- **Interval H&P every 3–6 mo for 2 y, every 6–12 mo for 3–5 y, then annually based on patient's risk of disease recurrence**
- **Cervical/vaginal cytology screening[s] as indicated for the detection of lower genital tract neoplasia**
- **Imaging as indicated based on symptoms or examination findings suspicious for recurrence[c]**
- **Laboratory assessment (CBC, blood urea nitrogen [BUN], creatinine) as indicated based on symptoms or examination findings suspicious for recurrence**
- **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 potential long-term and late effects of treatment (See NCCN Guidelines for Survivorship and NCCN Guidelines for Smoking Cessation)**

WORKUP

Clinically suspected recurrence → **• Imaging workup[c] • Consider biopsy to confirm local and/or distant recurrence**

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

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

[c] See 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. The likelihood of picking up asymptomatic recurrences by cytology alone is low.

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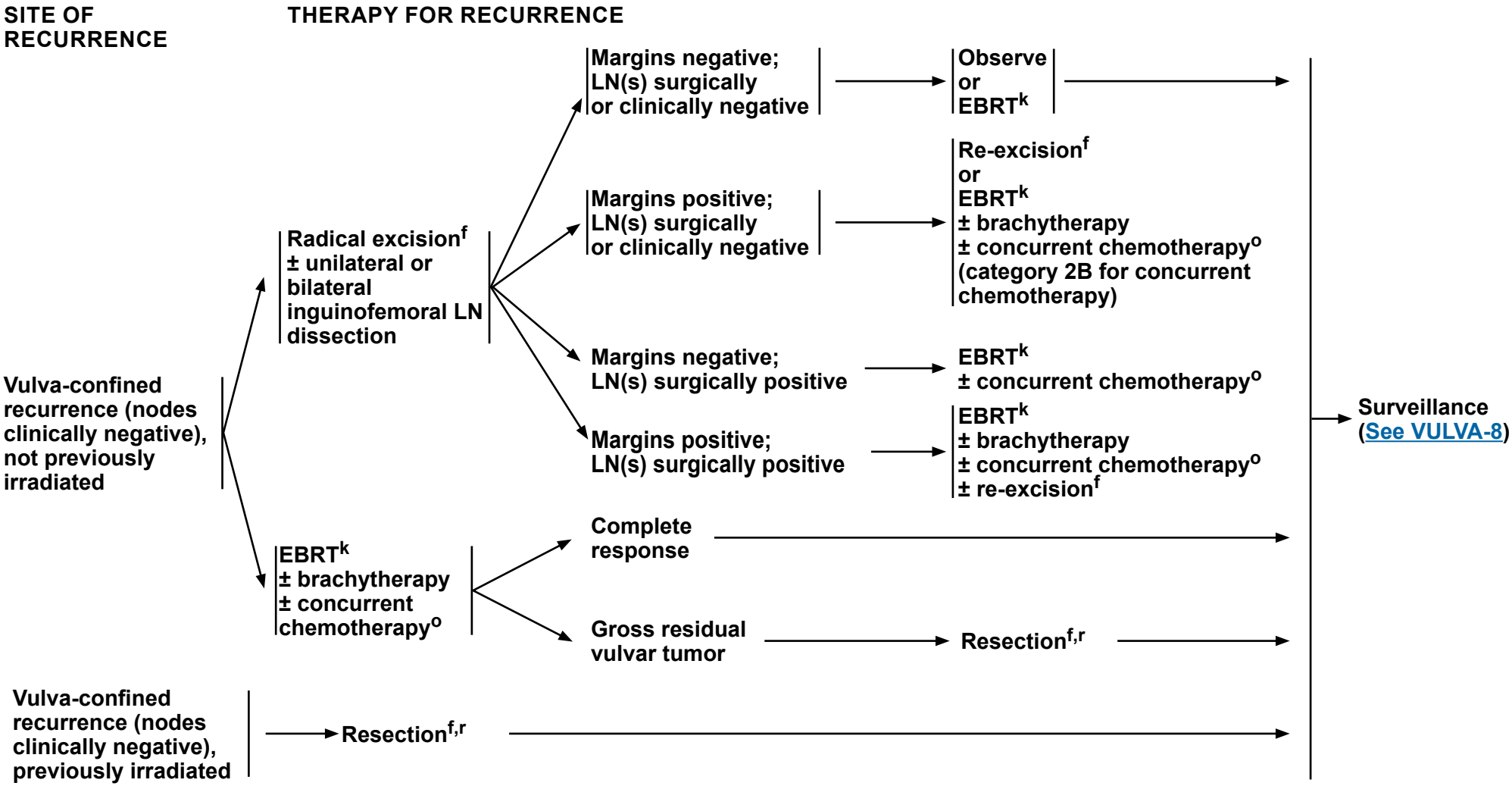

[f] See Principles of Surgery (VULVA-C).
[k] See Principles of Radiation Therapy (VULVA-D).
[o] See Systemic Therapy (VULVA-E).
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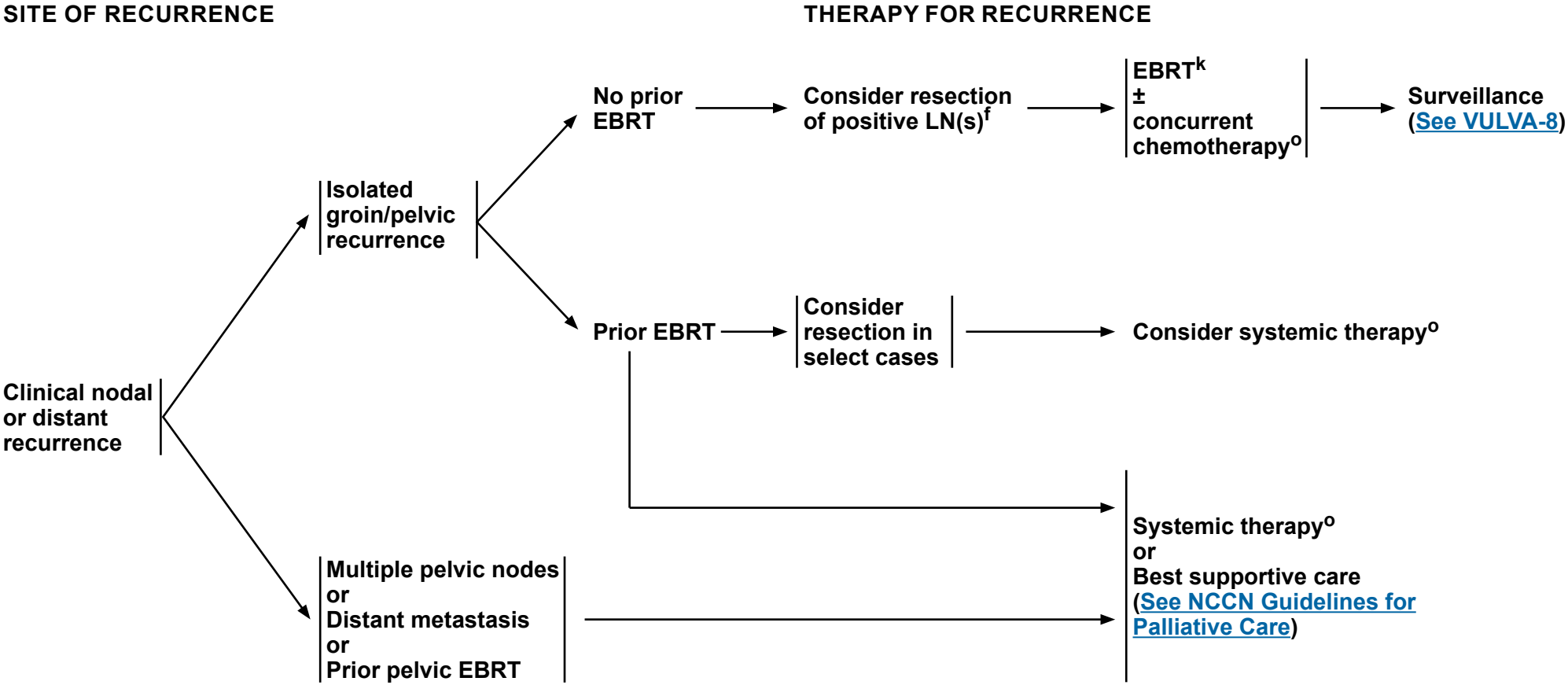

[f] See Principles of Surgery (VULVA-C).
[k] See Principles of Radiation Therapy (VULVA-D).
[o] See Systemic Therapy (VULVA-E).

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PRINCIPLES OF PATHOLOGY[1]

Procedure: Vulvectomy

Pathologic assessment for carcinoma:

- **Vulva**
  - **Procedure type (partial/total/radical vulvectomy)**
  - **Tumor site**
  - **Tumor size, include greatest dimension and additional two dimensions**
  - **Number of tumor foci**
  - **Histologic type**
  - **Histologic grade**
  - **Depth of invasion (in mm)[a]**
  - **Surgical resection margin status**
  - **Lymphovascular invasion**
- **Other tissue/organ involvement (vagina, urethra, anus, bladder mucosa, rectal mucosa, pelvic bone, other)**
- **Lymph nodes (when resected)**
  - **Sentinel lymph nodes should undergo ultrastaging for detection of low-volume metastasis[b]**
  - **Number of lymph nodes with:**
    - ◊ **Metastasis 5 mm or greater**
    - ◊ **Metastasis 5 mm or less**
    - ◊ **Isolated tumor cells (0.2 mm or less)**
- **Consider MMR/MSI testing for patients with recurrent, progressive, or metastatic disease**

Footnotes

[a]Depth of invasion is measured in millimeters from the epithelial-stromal junction of the adjacent, most superficial dermal papilla to the deepest point of invasion.

[b]Ultrastaging commonly entails thin serial sectioning of the gross sentinel lymph node and review of multiple H&E stained sections and cytokeratin immunohistochemistry for all blocks of sentinel lymph node. There is not a standard protocol for lymph node ultrastaging.

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.

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PRINCIPLES OF IMAGING[a,1-5]

Initial Workup

- **Consider chest imaging with plain radiography (chest x-ray). If an abnormality is seen, then chest CT without contrast may be performed.**
- **Consider pelvic MRI to aid in surgical and/or radiation treatment planning.[b]**
- **Consider whole body PET/CT or chest/abdomen/pelvic CT for T2 or larger tumors or if metastasis is suspected.[b]**
- **Other initial imaging should be based on symptomatology and clinical concern for metastatic disease.[b]**

Follow-up/Surveillance

- **CT chest/abdomen/pelvis or whole body PET/CT if recurrence/metastasis is suspected.[c]**
- **Other imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease.[c]**

Imaging for Documented Recurrence

- **Consider whole body PET/CT if not previously performed during surveillance.**
- **Consider pelvic MRI to aid in further treatment planning.**

Footnotes

[a]MRI and CT are performed with contrast throughout the guidelines 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. Gynec 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. Multimodlity imaging of vulvar cancer: staging, therapeutic response, and complications. AJR AM J Roentgenol 2013; 200:1387-1400.

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PRINCIPLES OF SURGERY: TUMOR MARGIN STATUS

- **Studies suggest a high overall incidence of local recurrence in vulvar carcinoma.[1] Tumor margin of resection has been postulated as a significant prognostic factor for recurrence in squamous cell carcinoma (SCC) of the vulva.[2,3]**
- **Efforts should be made to obtain adequate surgical margins (1–2 cm) at primary surgery.**
- **In the setting of a close or positive surgical tumor margin, re-resection may be considered to obtain wider margins.[4] Adjuvant local radiation therapy (RT) is another alternative.[5] The risk-benefit ratio and morbidity of these approaches must be considered and individualized in each patient.**
- **Close or 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-resection 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.**
- **Pathologists often have a challenging time assessing the presence and depth of invasion in vulvar SCC. The depth of stromal invasion is currently defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion. Alternative ways to measure the depth of invasion have recently been proposed.[6]**

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Continued
References

PRINCIPLES OF SURGERY: SURGICAL STAGING

- Vulvar cancer is staged using the American Joint Committee on Cancer (AJCC) and the International Federation of Gynecology and Obstetrics (FIGO) staging systems (Table ST-1).[7,8]
- Staging involves complete surgical resection of the primary vulvar tumor(s) with at least 1-cm margins and either a unilateral or bilateral inguinofemoral lymphadenectomy, or an SLN biopsy in select patients. Inguinofemoral lymphadenectomy removes the LNs superficial to the inguinal ligament, within the proximal femoral triangle, and deep to the cribriform fascia.
- LN status is the most important determinant of survival.[9]
- 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.[10]
- The current standard involves resection of the vulvar tumor and LNs through separate incisions.[10]
- The choice of vulvar tumor resection technique depends on the size and extent of the primary lesion and may include radical local excision and modified radical vulvectomy.
- The depth of the resection is similar for both radical local excision and radical vulvectomy (ie, to the urogenital diaphragm).[11]
- There are no prospective trials comparing the resection techniques above. Retrospective data suggest there is no difference in recurrence outcome between radical local excision compared with radical vulvectomy.
- For a primary vulvar tumor that is <4 cm, located 2 cm or more from the vulvar midline and in the setting of clinically negative inguinofemoral LNs, a unilateral inguinofemoral lymphadenectomy or SLN biopsy is appropriate (See Principles of Surgery: Inguinofemoral Sentinel Lymph Node Biopsy VULVA-C 3 of 4).[12]
- For a primary vulvar tumor located within 2 cm from or crossing the vulvar midline, a bilateral inguinofemoral lymphadenectomy[12] or SLN biopsy is recommended.
- Lymphadenectomy or SLN evaluation can be omitted in patients with stage IA primary disease with clinically negative groins due to a <1% risk of lymphatic metastases.[12]
- For patients with stage IB-II disease, inguinal lymphadenectomy is recommended due to a risk of >8% of lymphatic metastases.[12]
- A negative unilateral lymphadenectomy is associated with a <3% risk of contralateral metastases.[13]
- In the setting of positive LN disease after unilateral lymphadenectomy, contralateral lymphadenectomy[9] or radiation of the contralateral groin is recommended. Any nodes that are grossly enlarged or suspicious for metastases during the unilateral lymphadenectomy should be evaluated by frozen section pathology intraoperatively in order to tailor the extent and bilaterality of the LN dissection.
- 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.[12]
- The management of bulky inguinofemoral LNs in the setting of an unresectable or T3 primary vulvar lesion is unclear. It is reasonable to consider either: 1) primary cytoreductive surgery of the bulky LNs followed by platinum-based chemosensitizing radiation to the bilateral groins and primary vulvar tumor; or 2) platinum-based chemosensitizing radiation to the bilateral groins and primary vulvar tumor alone.[14]

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Continued
References

PRINCIPLES OF SURGERY: INGUINOFEMORAL SENTINEL LYMPH NODE BIOPSY

- Unilateral or bilateral inguinal 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.[15,16]
- Increasing evidence suggests that the use of SLN biopsy of the inguinofemoral LN basin is an alternative standard-of-care approach to lymphadenectomy in select women with SCC of the vulva.[17,18]
- SLN biopsy results in decreased postoperative morbidity without compromising detection of LN metastases.[17,19]
- 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.[17,18]
- Candidates for SLN biopsy include patients with negative clinical groin examination and imaging, a primary unifocal vulvar tumor size of <4 centimeters, and no previous vulvar surgery that may have impacted lymphatic flow to the inguinal region.[18,20,21]
- If SLN biopsy is considered, it ideally should be performed by a high-volume SLN surgeon, as high-volume surgeons exhibit improved SLN detection rates.[18]
- Increased sensitivity of SLN detection is observed when both radiocolloid and dye are used.[17,18,19] 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 dye most commonly used is Isosulfan Blue 1%. Approximately 3–4 cc of dye is injected peritumorally using a four-point injection technique at 2, 5, 7, and 10 o'clock. The dye is injected intradermally in the operating room within 15–30 minutes of initiating the procedure.
- 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 inguinal 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.
- 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 complete inguinofemoral lymphadenectomy is recommended if an ipsilateral SLN is not detected.
- The management of positive SLNs is currently being evaluated and may include performance of complete inguinofemoral lymphadenectomy and/or administration of adjuvant radiation to the affected groin(s).
- If ipsilateral SLN is positive, the contralateral groin should be evaluated surgically and/or treated with EBRT.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
References

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PRINCIPLES OF RADIATION THERAPY

General Principles

- **RT is often used in the management 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 anti-fungal 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.**

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Continued
References

PRINCIPLES OF RADIATION THERAPY

Treatment Information – 3D Conformal/Anterior-Posterior (AP/PA) Fields

- **Target Volumes**
  - **The target is best defined by both physical examination and CT-based treatment planning; contouring of the target structures is recommended. When an AP/PA technique is primarily used, often wide AP and narrower PA fields are used with electrons supplementing the dose to the inguinal region if the depth of the inguinal nodes allows for electron coverage. More conformal techniques such as three- or four-field approaches may allow for greater sparing of bowel and/or bladder, depending on tumor extent and patient anatomy. CT or MRI planning, with possible image fusion technology, should be used to assure adequate dosing and coverage with contouring of the primary, and the inguinofemoral and iliac nodes. Radio-opaque markers should be placed on key landmarks at the time of simulation to assist in definition of the primary target volume.**
  - **The superior field border should be no lower than the bottom of the sacroiliac joints or higher than the L4/L5 junction unless pelvic nodes are involved. If pelvic nodes are involved, the upper border can be raised to 5 cm above the most cephalad-positive node. The superior border should extend as a horizontal line to cover the inguinofemoral nodes at the level of the anterior-inferior iliac spine. The lateral border will be a vertical line drawn from the anterior-inferior iliac spine. To adequately cover the inguinal nodes, the inferio-lateral inguinal nodal border should be parallel to the inguinal crease and inferior enough to encompass the inguinofemoral nodal bed to the intertrochanteric line of the femur or 1.5–2 cm distal to the saphenofemoral junction. The inferior vulvar border will be lower and should be at least 2 cm below the most distal part of the vulva. Care should be taken to spare the femoral heads and necks.**

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Continued
References

PRINCIPLES OF RADIATION THERAPY

Treatment Information – Intensity-Modulated Radiation Therapy (IMRT)

- 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 clinical target volume (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.[4]

General Treatment Information

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

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Continued
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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 approaches or IMRT as long as care is given to assure adequate dosing and coverage of tissues at risk for tumor involvement.[1,5]**
- **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.**
- **Suggested dosing to areas of risk:**
  - **Gross primary disease = 60–70 Gy**
  - **Primary surgical bed (post op, negative margins) = 45–50 Gy**
  - **Uninvolved LNs = 45–50 Gy**
  - **Inguinal LNs (positive, R0) = 50–55 Gy**
  - **Inguinal LNs (extracapsular extension [ECE]) = 54–64 Gy**
  - **LNs (gross unresectable disease) = 60–70 Gy**

Continued

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References

PRINCIPLES OF RADIATION THERAPY
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SYSTEMIC THERAPY[1]

Chemoradiation	Chemotherapy for Advanced, Recurrent/Metastatic Disease
• **Preferred Regimens** ▸ **Cisplatin** • **Other Recommended Regimens** ▸ **Fluorouracil/mitomycin-C**[2] ▸ **Cisplatin/fluorouracil**	• **Preferred Regimens** ▸ **Cisplatin** ▸ **Carboplatin** ▸ **Cisplatin/paclitaxel** ▸ **Carboplatin/paclitaxel** ▸ **Cisplatin/paclitaxel/bevacizumab** • **Other Recommended Regimens** ▸ **Paclitaxel** ▸ **Cisplatin/vinorelbine** ▸ **Erlotinib (category 2B)**[3] ▸ **Cisplatin/gemcitabine (category 2B)** ▸ **Carboplatin/paclitaxel/bevacizumab (category 2B)** • **Useful In Certain Circumstances** ▸ **Pembrolizumab (second-line therapy for PD-L1–positive**[4] **or MSI-H/dMMR tumors)**

[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]Anal cancer literature supports the use of mitomycin-based regimens based on high-quality evidence. Chin JY, Hong TS, Ryan DP. Mitomycin in anal cancer: still the standard of care. J Clin Oncol 2012;30:4297-4301.
[3]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.
[4]Recommended for disease progression on or after chemotherapy in patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Staging-Vulvar Cancer

Table 1. **AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Carcinoma of the Vulva**

T	FIGO Stage	Primary Tumor
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	**I**	Tumor confined to the vulva and/or perineum. Multifocal lesions should be designated as such. The largest lesion or the lesion with the greatest depth of invasion will be the target lesion identified to address the highest pT stage. Depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
T1a	**IA**	Lesions 2 cm or less, confined to the vulva and/or perineum, and with stromal invasion of 1.0 mm or less
T1b	**IB**	Lesions more than 2 cm, or any size with stromal invasion of more than 1.0 mm, confined to the vulva and/or perineum
T2	**II**	Tumor of any size with extension to adjacent perineal structures (lower/distal third of the urethra, lower/distal third of the vagina, anal involvement)
T3	**IVA**	Tumor of any size with extension to any of the following—upper/proximal two thirds of the urethra, upper/proximal two thirds of the vagina, bladder mucosa, or rectal mucosa—or fixed to pelvic bone

Continued

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Staging-Vulvar Cancer

Table 1. **(continued)**

N	FIGO Stage	Regional Lymph Nodes
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	**III**	Regional lymph node metastasis with one or two lymph node metastases each less than 5 mm, or one lymph node metastasis greater than or equal to 5 mm
N1a*	**IIIA**	One or two lymph node metastases each less than 5 mm
N1b	**IIIA**	One lymph node metastasis greater than or equal to 5 mm
N2		Regional lymph node metastasis with three or more lymph node metastases each less than 5 mm, or two or more lymph node metastases greater than or equal to 5 mm, or lymph node(s) with extranodal extension
N2a*	**IIIB**	Three or more lymph node metastases each less than 5 mm
N2b	**IIIB**	Two or more lymph node metastases greater than or equal to 5 mm
N2c	**IIIC**	Lymph node(s) with extranodal extension
N3	**IVA**	Fixed or ulcerated regional lymph node metastasis

M	FIGO Stage	Distant Metastasis
M0		No distant metastasis (no pathological M0; use clinical M to complete stage group)
M1	**IVB**	Distant metastasis (including pelvic lymph node metastasis)

G	Histologic Grade
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

*Includes micrometastasis, N1mi and N2mi.
Note: The site, size, and laterality of lymph node metastases should be recorded.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus 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.

Table of Contents

Overview

In 2018, an estimated 6190 women will be diagnosed with vulvar cancer, and 1200 are expected to die from the disease.[1] Vulvar cancer accounts for 4% of gynecologic malignancies and median age of diagnosis is 68 years. Based on data from the SEER database, 5-year survival rates range from 86% for localized disease (stages I/II), to 53% for regional or locally advanced disease (stages III/IVA), and finally to 19% 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 in recent years. In 2004, vulvar intraepithelial neoplasia (VIN) terminology was refined to include 2 types of lesions, usual-type VIN and differentiated VIN.[8] Usual-type VIN was linked to persistent infection with carcinogenic strains of HPV, while differentiated VIN 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) differentiated VIN.[9]

Estimates of the percentage of vulvar cancers attributable to HPV infection range from conservative estimates of 30% to up to 69%, with a recent meta-analysis reporting an HPV prevalence of 39.7%.[10-13] However, HPV infection is detected in 80% to 90% of HSIL. Historically, VIN has been diagnosed in younger women (median age 45–50 years) while vulvar cancers have been diagnosed in older women (median age 65–70 years).[14,15] 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.[10,14]

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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the creation of this version of the NCCN Guidelines® for Vulvar Cancer, an electronic search of the PubMed database was performed to obtain key literature in cervical cancer published between 2017 and 2018, 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 Study; Meta-Analysis; Observational Studies; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 112 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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

Diagnosis and Workup

Currently, these guidelines focus on the diagnosis, evaluation, and treatment of vulvar SCC. At this time, the guidelines do not address the evaluation and management of rare, non-SCC histologies. For the purposes of this discussion, vulvar SCC will be generally referred to as "vulvar cancer."

These guidelines utilize the FIGO (International Federation of Gynecology and Obstetrics) and American Joint Committee on Cancer (AJCC) TNM staging systems, which closely align for the staging of vulvar cancer. The FIGO system was updated in 2009;[16,17] the 8th edition of the AJCC Cancer Staging Manual was released in 2017.[18] In the updated FIGO system, major changes include the combination of former elements of stage I, II, and III, redefinition of stage III to include only those with positive groin nodes (with subclassification based on the number/size of involved nodes), and shifting away from the previous focus on bilateral lymph node involvement. Patients with positive pelvic nodes, even without distant visceral metastasis, are considered stage IVB.[16] The impact of this revised classification system has been examined.[19-21]

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, 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.[14,15,22] Although many cases may be asymptomatic, pruritus and pain/irritation is a common symptom; vulvar bleeding or discharge may also occur. A majority of patients present with early-stage (ie, 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://cap.objects.frb.io/protocols/cp-femalereproductive-vulva-18protocol-4100.pdf). This CAP protocol was revised in August 2018 and reflects recent updates in the AJCC/FIGO staging.

Workup includes history and physical examination, complete blood count (CBC), and liver and renal function tests. In additional 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.[23-27] Examination-under-anesthesia (EUA) cystoscopy or proctoscopy should be considered as indicated. Appropriate patients should receive smoking cessation counseling and HPV testing. Consider HIV testing, especially in younger patients.

Prognostic Factors

Historically, en bloc vulvectomy with wide margins was combined with complete inguinofemoral 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.[22] 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 lymph nodes, as well as primary tumor size.[28] Lymph node metastasis is considered the most important prognostic factor and determinant of treatment in vulvar cancer,[29,30] and extracapsular extension has been linked to poorer prognosis.[31-34] 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).[14,28,35-40] However, these findings are primarily derived from retrospective analyses. A recent 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.[41]

Prognostic data have guided the shift towards more conservative primary tumor resection and regional lymph node management for early-stage disease.[42] The preferred surgical approach evolved towards vulvar-sparing techniques with separate incisions for lymph node dissection in patients who were clinically node negative.[22,43] Current surgical approaches involve tailored primary tumor resection and lymph node evaluation based on individual patient characteristics.[44,45] Data suggest that survival is not negatively impacted by less radical surgical approaches for early-stage cancers.[45]

Surgical Staging

The AJCC and FIGO systems stage vulvar cancer according to extent of primary tumor (T), lymph node status (N), and distant metastasis (M). Clinical staging alone provides inadequate evaluation of lymph node involvement. Because lymph node metastasis is a key prognostic factor in vulvar cancer survival,[29,45] these systems use 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 inguinofemoral lymphadenectomy. However, common practice has increasingly included the use of sentinel lymph node (SLN) biopsy in lieu of complete lymph node dissection, as well as diagnostic imaging to determine extent of disease.[46,47]

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, local excision/wide excision, partial/total/radical vulvectomy). 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 lymphovascular invasion. When resected, the number of lymph nodes 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.

Primary Tumor Resection

Depending on the size and extent of the primary tumor, radical local excision or modified radical 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.[48-50] 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 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.[35,38,51] A recent 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 ≤5 mm.[52] The goal of primary tumor resection is complete removal with 1- to 2-cm margins. In the setting of close or positive tumor margins, re-resection to obtain adequate margins or adjuvant local radiation therapy (RT) are options.[35,53] In a recent study, tumor-free margins of at least 2 mm were associated with lower local recurrence risk.[39]

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.[54] 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 lymph node status is the most important determinant of survival in vulvar cancer, careful evaluation and determination of nodal status is paramount. Lymph node resection is performed through a separate incision from the primary tumor and may entail unilateral or bilateral inguinofemoral lymphadenectomy, or SLN biopsy in select cases. Inguinofemoral lymphadenectomy involves removal of superficial inguinal and deep femoral lymph nodes. Further emphasizing the importance of adequate inguinofemoral 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.

Lymph node dissection in patients with clinically negative groin nodes is informed by the size and location of the primary tumor. Because the risk of lymph node metastasis is less than 1% in patients with stage IA disease,[44] lymphadenectomy or SLN evaluation can be omitted in patients with stage IA (T1A and N0 tumors) primary disease with clinically negative groins. However, inguinofemoral 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.[44] For primary vulvar tumors <4 cm in diameter, located at least 2 cm from the vulvar midline, with clinically negative IFLNs, unilateral inguinofemoral lymphadenectomy, or SLN biopsy are appropriate.[55,56] However, bilateral lymph node evaluation (full dissection or SLN biopsy, if indicated) is recommended for patients with primary tumors that are within 2 cm of, or crossing, the vulvar midline.[56] 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 inguinofemoral lymphadenectomy are high. An estimated 20% to 40% of patients have wound complications and 30% to 70% of patients experience lymphedema.[57-59] Studies have begun to investigate whether complete inguinofemoral 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-VI) of 403 women with primary vulvar tumors <4 cm. Inguinofemoral 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 dissection.[60]

In GOG 173, 452 women (with vulva-confined primary tumors 2 cm–6 cm, at least 1-mm invasion, and clinically node negative) underwent SLN mapping and biopsy followed by inguinofemoral lymphadenectomy. SLNs were identified in 418 women, and 132 women 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).[61]

A subgroup analysis of the AGO-CaaRE-1 study compared outcomes of patients with tumors <4 cm who underwent radical LN/SLN dissection with negative findings for LN/SLN metastasis (n = 556). The radical dissection 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 PFS and OS between the radical and SLN dissection cohorts.[63]

A recent 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 inguinofemoral lymphadenectomy, superficial inguinofemoral 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.[62]

The GROINSS-VI 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 inguinofemoral 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 >10 mm, suggesting no disease threshold below which further treatment of a SLN-positive groin could be safely omitted. Disease-specific survival (DSS) was worse among those with SLN metastases >2 mm versus ≤2 mm (69.5% vs. 94.4%, $P = .001$).[64] Patients undergoing SLN biopsy reported less treatment-related morbidity compared with those undergoing IFLN dissection.[65]

Long-term follow-up of the GROINSS-VI cohort compared outcomes of SLN-positive patients who underwent completion IFLN dissection with those of SLN-negative patients (no IFLN dissection). 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 patients with a positive SLN ($P = .03$). 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.[66]

The ongoing GROINSS-VII/GOG 270 study (NCT01500512) is comparing radiotherapy of the groin with groin node dissection among patients with SLN metastases.

Panel Recommendations

For appropriate individuals, the panel considers SLN mapping and biopsy of the IFLN basin a reasonable alternative approach to decrease postoperative morbidity while maintaining a low of groin recurrences with this surgical approach in vulvar cancer.[60,61,64]

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.[62,64] 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.[61,62] The panel recommends complete inguinofemoral 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 primary tumor diameter ≤2 cm and depth of invasion ≤5 mm and with a clinically negative contralateral groin examination, a contralateral groin dissection or radiation may be omitted.[67]

Primary Treatment

For the purposes of primary treatment, these guidelines provide treatment recommendations by clinical stage, separating patients into those with early-stage (stage I/II), locally advanced (stage III/IVA/IVB with pelvic-confined disease), and distant metastatic disease (extrapelvic stage IVB). Patients with early-stage disease include those with T1 or smaller T2 primary tumors; smaller T2 primary tumors are classified as ≤4 cm with no/minimal involvement of the urethra, vagina, or anus. Patients with locally advanced disease include those with larger T2 (>4 cm and/or involvement of the urethra, vagina, or anus) or T3 primary tumors for whom visceral-sparing primary surgery is not indicated. Patients with distant metastatic disease may fall within any “T” or “N” classification.

Early-Stage Disease

After careful clinical evaluation and staging, the standard primary treatment of early-stage vulvar SCC is conservative, individualized tumor excision with IFLN evaluation.[43,49,68-71] Clinicians should strive for primary tumor resection with oncologically appropriate margins of 1 to 2 cm if feasible.[35,38,51,53] 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.[49,50]

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.[72] 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.[73] Primary radiation may have some benefit for those unable to undergo surgery.[74,75]

Panel Recommendations

For T1 tumors with ≤1 mm depth of invasion (pT1A), the panel recommends wide local resection or radical local resection; IFLN evaluation is not required due to the low risk of lymph node metastasis in these patients.[44,69,76-79] 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 T1b or smaller T2 tumors that have a depth of invasion in excess of 1 mm, primary treatment is dictated by tumor location. Patients with lateralized lesions (>1 mm invasion) located ≥2 cm from the vulvar midline should undergo radical local resection or modified radical vulvectomy accompanied by ipsilateral groin node evaluation.[55,56,76]

Groin evaluation can be performed through SLN biopsy or ipsilateral IFLN dissection. Dissection should be performed if no SLN(s) is/are detected. Adjuvant therapy is informed by primary tumor and nodal surgical pathology. Patients with midline vulvar lesions (>1-mm invasion) should undergo radical local resection or modified radical vulvectomy accompanied by bilateral groin node evaluation consisting of SLN biopsy or ipsilateral IFLN dissection.[49,56,76] Groin dissection is required on side(s) for which sentinel nodes are not detected. Adjuvant therapy is informed by primary tumor and nodal surgical pathology.

Locally Advanced Disease

Historically, locally advanced vulvar cancers were treated primarily with radical surgeries such as en bloc radical vulvectomy with bilateral inguinofemoral 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.[22,80-82] Additionally, complete resection of locally advanced disease may be complicated by tumor fixed to vital organs or vessels, rendering the disease unresectable.[83] A shift to multimodality treatment was explored to improve organ preservation and reduce surgical treatment morbidity.[84] Preoperative RT was shown in some earlier studies to result in tumor debulking and reduce the extent of surgery required for locally advanced disease.[83,85-88] 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,[89-93] with several studies revealing complete tumor responses among more than 60% of the cohort.[94-98]

Primary chemoradiation may confer a survival benefit over primary RT in vulvar cancer. Overall survival (OS) after primary chemoradiation was superior to OS following primary RT in a series of 54 patients with locally advanced disease.[99] A similar survival benefit was recently 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 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).[100]

In the GOG 101 study, preoperative chemoradiation was examined in 73 patients with stage III/IV disease.[91] 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 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.[101] 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 36/37 patients and for the primary tumor in 29/38 patients. More recently, 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.[102] Complete clinical response was noted in 64% of patients (37/58), with complete pathologic response in 78% (29/34) of patients undergoing surgical biopsy. The high pathologic complete response (pCR) rates have led many to believe that surgery can be avoided in locally advanced tumors who achieve clinical complete responses.

An analysis of NCDB data (2004–2012) compared outcomes of 2046 women with locally advanced vulvar cancer that 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.[103]

A 2011 Cochrane database review of the existing randomized controlled trial data on 141 women with locally advanced vulvar SCC revealed no difference in OS when comparing primary surgery to primary or neoadjuvant chemoradiation.[104] 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 5 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.[105]

The combination regimen used for radiosensitization was most commonly cisplatin/5-FU,[91,92,94,96,97] but also included 5-FU/mitomycin C[90,93,98] or single-agent therapy.[95,102] The selection of radiosensitizing chemotherapy is often based on extrapolation of findings from cervical, anal, or head and neck cancer.

Panel Recommendations

Patients with larger T2 (>4 cm and/or involvement of the urethra, vagina, or anus) or T3 tumors should undergo radiologic imaging if not previously performed to examine potential nodal involvement. The panel recommends that all patients with locally advanced disease receive EBRT with concurrent chemotherapy. IFLN dissection may be used to assess nodal metastasis to inform RT treatment planning.

If IFLN dissection is not performed, or if positive IFLNs are found upon dissection, EBRT coverage should include the primary tumor, groin, and pelvis. If no positive nodes are detected following inguinofemoral lymphadenectomy, EBRT with concurrent chemotherapy should be provided with RT coverage of the primary tumor, with or without selective coverage of groin lymph nodes.

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

Agents recommended by the panel for chemoradiation include cisplatin (preferred), 5-FU/cisplatin, or 5-FU/mitomycin-C.[106,107]

Metastasis Beyond the Pelvis

Data on systemic treatments for vulvar SCC with distant metastasis are extremely limited.[108-110] 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.

Panel Recommendations

Primary treatment options for extra-pelvic metastatic disease include EBRT for control of locoregional disease and symptom control, and/or systemic therapy. Best supportive care is also an alternative in this setting. Preferred regimens recommended by the panel for treating advanced, recurrent/metastatic disease include cisplatin and carboplatin as single agents, as well as cisplatin/paclitaxel, carboplatin/paclitaxel, and cisplatin/paclitaxel/bevacizumab. Other recommended regimens include single-agent paclitaxel or erlotinib (category 2B for erlotinib), cisplatin/vinorelbine, cisplatin/gemcitabine (category 2B), or carboplatin/paclitaxel/bevacizumab (category 2B). Pembrolizumab is a recommended regimen that is useful in certain circumstances (ie, PD-L1-positive or MSI-H/dMMR tumors).

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 lymph node involvement is a critical prognostic factor in vulvar SCC, the optimal patient selection criteria and adjuvant therapy regimens to address nodal disease continue to be determined.[111] 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 groin node-positive vulvar cancer after radical vulvectomy and bilateral inguinofemoral lymphadenectomy.[112,113] Patients were randomized to receive pelvic node dissection 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 ≥2 positive groin nodes or those with fixed ulcerative groin 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).[113]

A recent study using SEER-Medicare–linked data examined outcomes for 444 elderly 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.[114]

There are conflicting data on the benefit of adjuvant RT in patients with a single positive lymph node. Some studies in patients with a single positive lymph node have reported no benefit of adjuvant RT in this setting.[115,116] 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.[117] 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 >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.[118]

The large, multicenter, retrospective AGO-CaRE-1 study reported significant survival benefits in node-positive patients receiving adjuvant RT or chemoradiation (3-year progression-free survival [PFS] of 39.6% vs. 25.9%, *P* = .004; 3-year OS of 57.7% vs. 51.4%, *P* = .17).[116] 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 ≥2 positive lymph nodes.

When adjuvant RT to the lymph nodes is delivered, care should be used to avoid excessive blocking of the central pelvic structures.[119]

Recent 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).[120] Based on SEER data, outcomes of adjuvant RT were examined in 519 patients aged 66 years and older who received primary surgery for node-positive vulvar cancer. Adjuvant RT was associated with improved OS over surgery alone in this cohort of older women (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).[121] Parameters for delivery of RT were important among this cohort; 3-year OS and CSS were significantly improved in patients who received ≥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.[122] 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 ≥56 Gy compared with those receiving ≤50.4 Gy.[52]

Panel Recommendations

For patients with early-stage disease (T1) and a depth of invasion ≤1 mm (pT1a), observation is appropriate following primary surgery. For patients with T1b and T2 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.[60,123-126] Adjuvant therapy is warranted if the SLN or IFLNs contain metastases. Adjuvant therapy for patients with SLN involvement includes: 1) RT with or without concurrent chemotherapy; or 2) completion IFLN dissection followed by EBRT with or without concurrent chemotherapy. Adjuvant therapy for patients who have positive IFLNs detected during groin node dissection includes EBRT (category 1) with or without concurrent chemotherapy. Chemoradiation is strongly recommended for patients with two or more positive IFLNS or a single IFLN with >2-mm metastasis.[112,116]

In additional to nodal status, a number of primary tumor risk factors may influence adjuvant therapy decisions. These include close tumor margins, LVSI, tumor size, depth of invasion, and pattern of invasion (spray vs. diffuse). Observation is reasonable in the setting of negative primary tumor margins with no additional risk factors. Treatment of patients with primary tumor margins positive for noninvasive disease (eg, HSIL) should be individualized. If surgical margins are positive for invasive disease, re-excision should be considered to achieve oncologically appropriate margins. Patients with continued positive margins after re-excision should receive adjuvant EBRT.[122] Patients with oncologically appropriate margins following re-excision may be candidates for observation unless additional risk factors warrant adjuvant EBRT. For patients with positive margins for invasive disease who are not candidates for re-excision, adjuvant EBRT should be offered.

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 IFLN dissection). 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 one to two years, although recurrences beyond 5 years have been observed in a significant subset of patients.[127,128] Accordingly, long-term follow-up is indicated. Definitive data on an optimal surveillance strategy are lacking.[129] However, the panel concurs with the updated Society of Gynecologic Oncology recommendations for post-treatment surveillance.[130]

The recommended surveillance is based on the patient's risk for recurrence and personal preferences. History and physical examination is 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 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. Imaging (ie, chest radiography, CT, PET/CT, 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, and depression), see the NCCN Guidelines for Survivorship. Smoking cessation and

abstinence should be encouraged; see the NCCN Guidelines for Smoking Cessation (www.NCCN.org).

Sexual dysfunction and low body image are unfortunately common among women who have undergone vulvectomy and/or RT of the groin/pelvis.[59,131,132] Patients who received RT for vulvar cancer may experience vaginal stenosis and dryness and should receive education on important issues regarding sexual health and vaginal health. Providers should inform patients about regular vaginal intercourse and/or vaginal dilator use and on the use of vaginal moisturizers/lubricants (eg, estrogen creams as well as non-hormonal options). Anecdotal evidence suggests that vaginal dilators may be used to prevent or treat vaginal stenosis. Dilator use can start 2 to 4 weeks after RT is completed and can be performed indefinitely (https://www.mskcc.org/clinical-updates/improving-women-s-sexual-health-after-cancer-treatment).

If persistent or recurrent disease is suspected, patients should be evaluated using additional imaging studies and biopsy 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.[30] 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.[133] Treatment approach and patient outcomes depend on the site and extent of recurrent disease.[133,134] Isolated local recurrences can often be treated successfully with radical local excision,[30,128,135] and RT with or without chemotherapy provided some degree of DFS in several studies.[87,88] A retrospective review of patients with locoregional recurrences were managed with chemoradiation, neoadjuvant chemotherapy, or RT alone. Five-year DFS and OS were around 20%; however, those with single-site recurrence and lesions ≤3 cm who received RT dose at or above 64.8 Gy remained disease-free at 5 years.[136] Conversely, another series noted decline in survival with the presence of nodal metastases, tumors >3 cm, or high-grade lesions.[137] For central/large recurrences, pelvic exenteration has been shown to prolong survival when performed on carefully selected patients.[80,81,138] Regardless of treatment approach, prognosis for nodal recurrences was very poor.[128,135,137,139,140]

Panel Recommendations

If recurrence is suspected, the panel recommends workup for metastatic disease with imaging studies to include chest/abdominal/pelvic CT or whole-body 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 radical excision ± unilateral or bilateral IFLN dissection. 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 with or without brachytherapy and/or concurrent chemotherapy (category 2B for chemotherapy). EBRT with or without

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, with or without brachytherapy, concurrent chemotherapy, and/or re-excision as needed/appropriate.

Nonsurgical therapy for recurrence includes EBRT with or without brachytherapy and/or concurrent chemotherapy. Resection can be considered for patients with gross residual tumor. When feasible, resection is also indicated for patients with vulva-confined recurrence who were previously irradiated. After treatment for recurrence, patients should undergo surveillance.

Nodal Recurrence or Distant Metastasis

Systemic therapy, palliative/best supportive care, or clinical trial enrollment is recommended for patients experiencing recurrence who received prior pelvic EBRT, and for patients with multiple positive pelvic nodes or distant metastasis. Resection followed by systemic therapy can be considered for select cases of isolated groin/pelvic recurrence that were previously irradiated.

If recurrence is limited to the groin and no prior RT was given, then consider resection of positive nodes followed by EBRT ± concurrent chemotherapy. For unresectable nodes, EBRT with or without concurrent chemotherapy is appropriate. All patients should undergo surveillance following treatment for recurrent disease.

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, as well as other SCCs. See the review article by Reade et al for an overview of systemic therapies that have been utilized to treat vulvar SCC.[106] Preferred regimens recommended by the panel for treating advanced, recurrent/metastatic disease include cisplatin and carboplatin as single agents, as well as cisplatin/paclitaxel, carboplatin/paclitaxel, and cisplatin/paclitaxel/bevacizumab. Other recommended regimens include single-agent paclitaxel or erlotinib (category 2B for erlotinib), cisplatin/vinorelbine, cisplatin/gemcitabine (category 2B), or carboplatin/paclitaxel/bevacizumab (category 2B). Pembrolizumab is a recommended regimen that is useful in certain circumstances, for PD-L1-positive or MSI-H/dMMR tumors.

Cisplatin (preferred) 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.[83,141] Cisplatin/paclitaxel and cisplatin/paclitaxel/bevacizumab are also preferred regimens based on extrapolation of randomized phase III trial data in advanced or recurrent/metastatic cervical cancer.[142,143]

Carboplatin is an alternative platinum agent active in metastatic cervical cancer that can be used as a single agent (preferred) or in combination. A small series in 6 patients with advanced or recurrent/metastatic vulvar cancer noted limited clinical benefit of the combination regimen;[108] 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.[144,145] Carboplatin-based combination regimens recommended in the guidelines include carboplatin/paclitaxel (preferred) and carboplatin/paclitaxel/bevacizumab (category 2B).

Single-agent paclitaxel was modestly active in a phase II trial of 31 women with advanced, recurrent/metastatic vulvar cancer, generating a response rate of 14% and PFS of 2.6 months.[109] Cisplatin/vinorelbine was studied in a small case series of patients with recurrent disease, producing a 40% response rate, 10-month PFS, and 19-month OS.[146] Erlotinib was studied

in a phase II trial that included a cohort of women with metastatic disease. Short-duration responses were observed, with partial responses and stable disease noted in 27.5% and 40% of enrolled patients, respectively.[110] Cisplatin/gemcitabine is also included as a category 2B option extrapolating from cervical cancer data; however, findings from case reports have been mixed.[147,148]

Pembrolizumab has been studied and is approved as a second-line therapy for PD-L1–positive or dMMR/MSI-H cervical cancers.[149-151] Based on these data, pembrolizumab is also included in these guidelines as a second-line therapy for PD-L1–positive or MSI-H/dMMR vulvar tumors. Early studies suggest that PD-L1–positive vulvar cancers could be candidates for anti-PD-1 therapy, and the ongoing KEYNOTE-158 trial is enrolling patients with advanced vulvar cancer to receive pembrolizumab therapy (NCT02628067).[152,153]

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