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Vulvar Cancer, Version 1.2017

Clinical Practice Guidelines in Oncology

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Overview

Vulvar cancer is a rare gynecologic malignancy. However, based on data from the SEER database, 5-year survival rates range from 86% for localized disease (stages I–II), to 57% for regional or locally advanced disease (stages III–IVA), and finally to 17% for patients with distant metastasis (stage IVB).[1] Vulvar cancer can arise through human papilloma virus (HPV)–dependent and HPV-independen-

Abstract

Vulvar cancer is a rare gynecologic malignancy. Ninety percent of vulvar cancers are predominantly squamous cell carcinomas (SCCs), which can arise through human papilloma virus (HPV)–dependent and HPV-independent pathways. The NCCN Vulvar Cancer panel is an interdisciplinary group of representatives from NCCN Member Institutions consisting of specialists in gynecological oncology, medical oncology, radiation oncology, and pathology. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Vulvar Cancer provide an evidence- and consensus-based approach for the management of patients with vulvar SCC. This manuscript discusses the recommendations outlined in the NCCN Guidelines for diagnosis, staging, treatment, and follow-up.

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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 noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Vulvar Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Vulvar Cancer Panel members can be found on page 120. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

dent pathways, the latter of which is more common in older women.[2]

Studies of the SEER database and the National Cancer Database have shown that treatment approaches/modalities vary considerably with sociodemographic factors such as race/ethnicity, age, and nonprivate insurance, particularly for patients with advanced disease.[3,4]

Ninety percent of vulvar cancers are of squamous cell carcinoma (SCC) histology.[2] Risk factors for the development of vulvar neoplasia include increasing age, infection with HPV, cigarette smoking, inflammatory conditions affecting the vulva, and immunodeficiency. Most vulvar neoplasias are diagnosed at early stages.[5] Although vulvar SCC is the most common type of vulvar cancer, rarer histologies exist and include melanoma, extramammary Paget disease, Bartholin gland adenocarcinoma, verrucous carcinoma, basal cell carcinoma, and sarcoma.[6]

The International Society for the Study of Vulvovaginal Disease (ISSVD) 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.[7] Usual-type VIN was linked to persistent infection with carcinogenic strains of HPV; differentiated VIN was commonly associated with vulvar dermatologic conditions such as lichen sclerosus. In 2015, the ISSVD updated the description to 3 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 *usual-type VIN*); and (3) differentiated VIN.[8]

Text cont. on page 108.

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†NCCN gratefully acknowledges the following NCCN Imaging Panel members for their contributions during the development of the Principles of Imaging (VULVA-A) in Version 1.2017 of the NCCN Guidelines for Vulvar Cancer:

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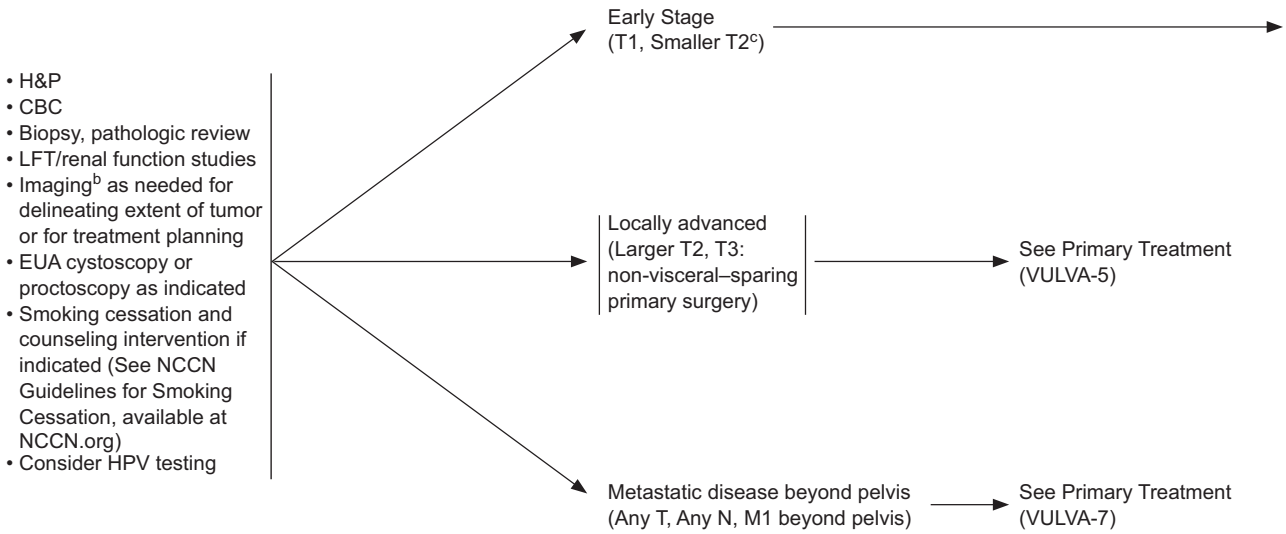
SQUAMOUS CELL CARCINOMA[a]

WORKUP

CLINICAL STAGE

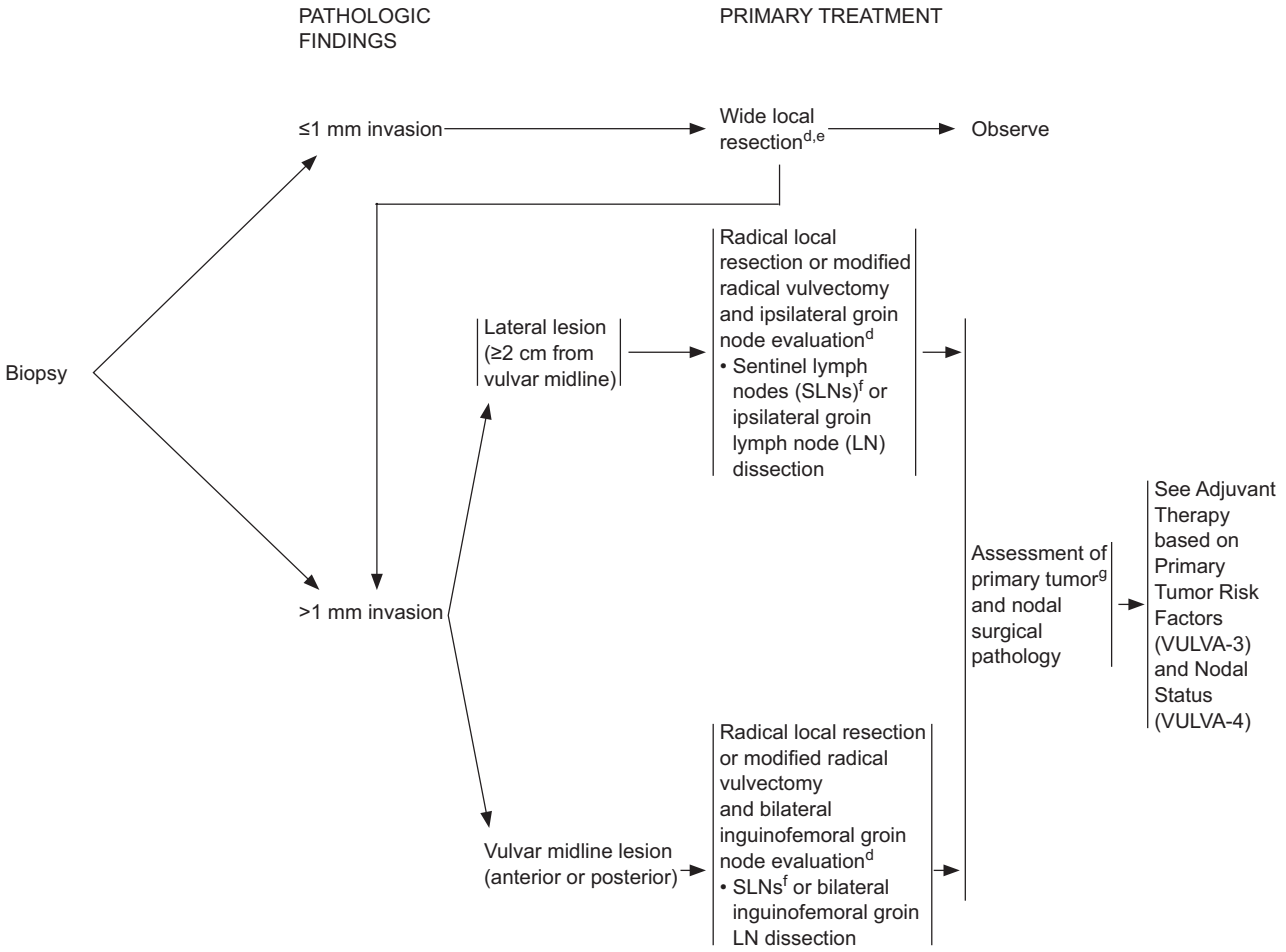
PRIMARY TREATMENT



[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 Imaging (VULVA-A).

[c]Smaller T2 tumors: ≤4 cm.



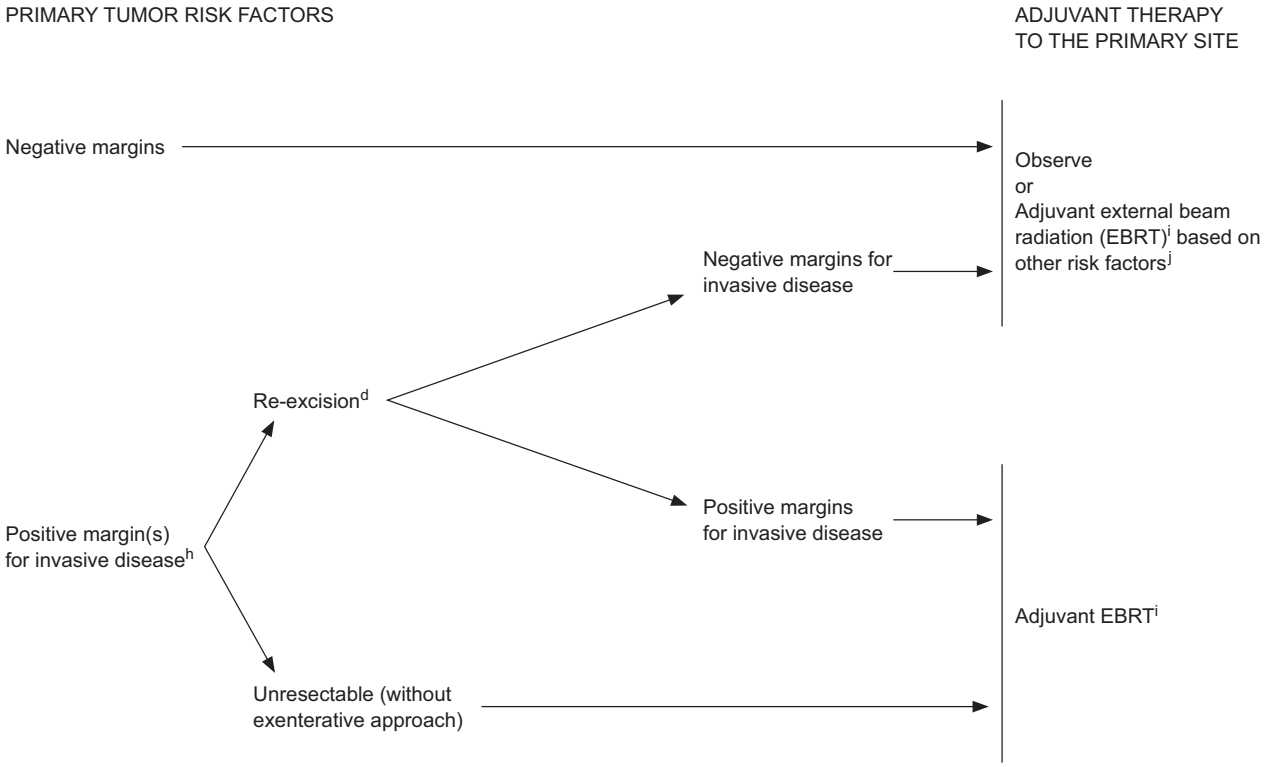
[c]Smaller T2 tumors: ≤4 cm.

[d]See Principles of Surgery (VULVA-B).

[e]If wide local resection pathology reveals tumor in aggregate of ≥1 mm invasion, then additional surgery may be warranted.

[f]Groin node dissection is required on side(s) where sentinel nodes are not detected.

[g]See Principles of Surgery: Tumor Margin Status (VULVA-B 1 of 4).



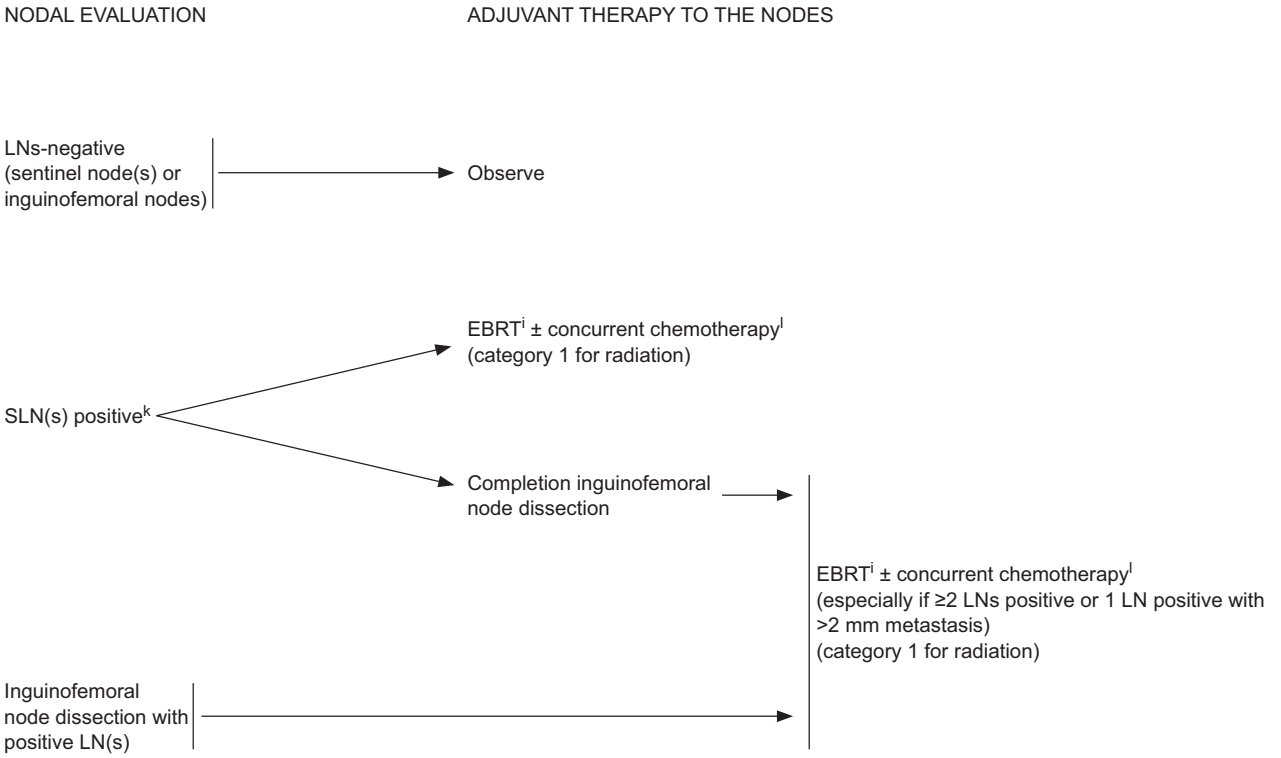
See Surveillance (VULVA-8)

[d]See Principles of Surgery (VULVA-B).

[h]The management of positive margins for HSIL (non-invasive disease) should be individualized.

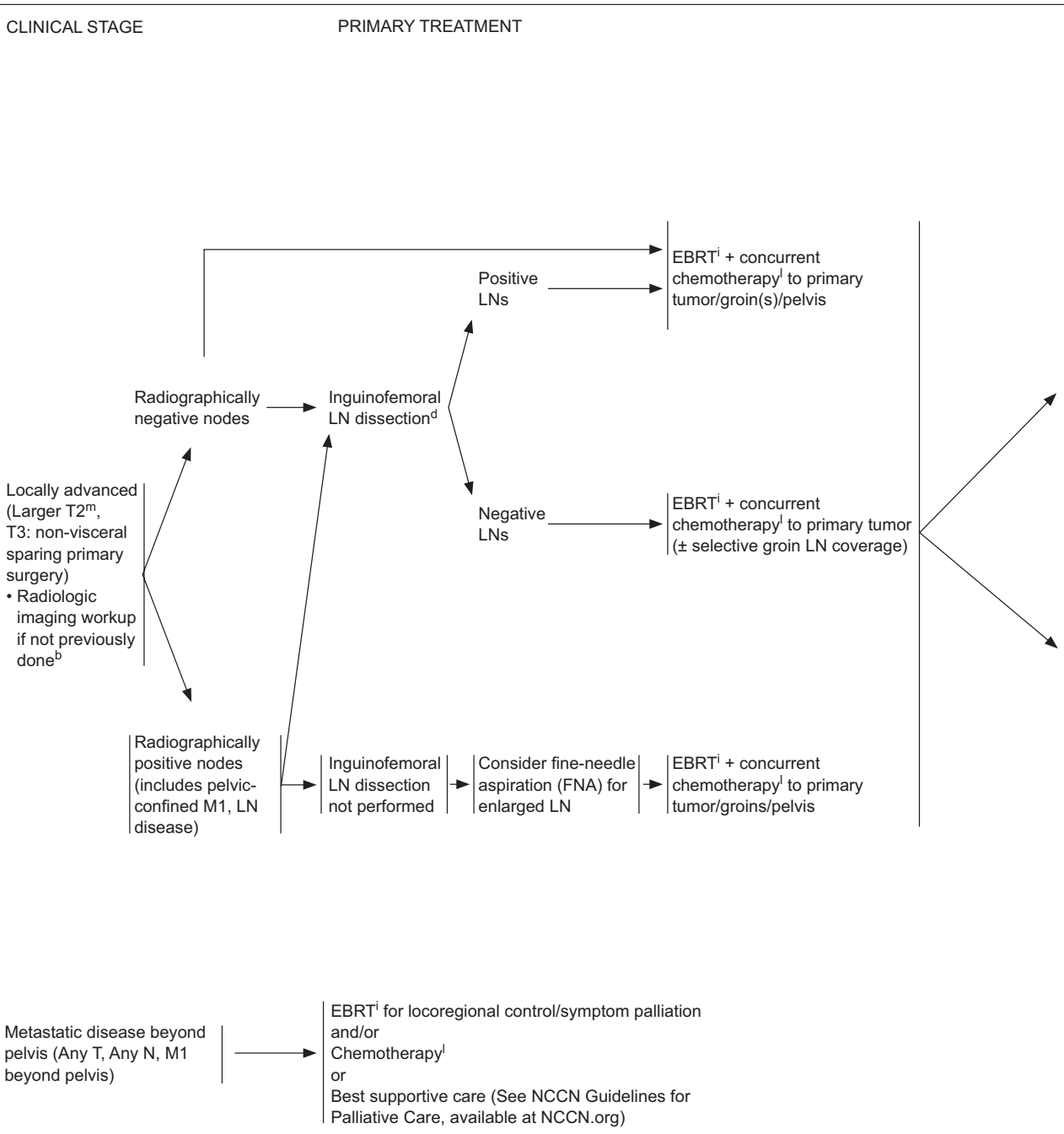
[i]See Principles of Radiation Therapy (VULVA-C).

[j]Other primary risk factors include: lymphovascular invasion, negative but close tumor margins (<8 mm), 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.



See Surveillance (VULVA-8)

[i]See Principles of Radiation Therapy (VULVA-C).
[k]See Principles of Surgery: Inguinofemoral Sentinel Lymph Node Procedure (VULVA-B 3 of 4).
[l]See Systemic Therapy (VULVA-D).

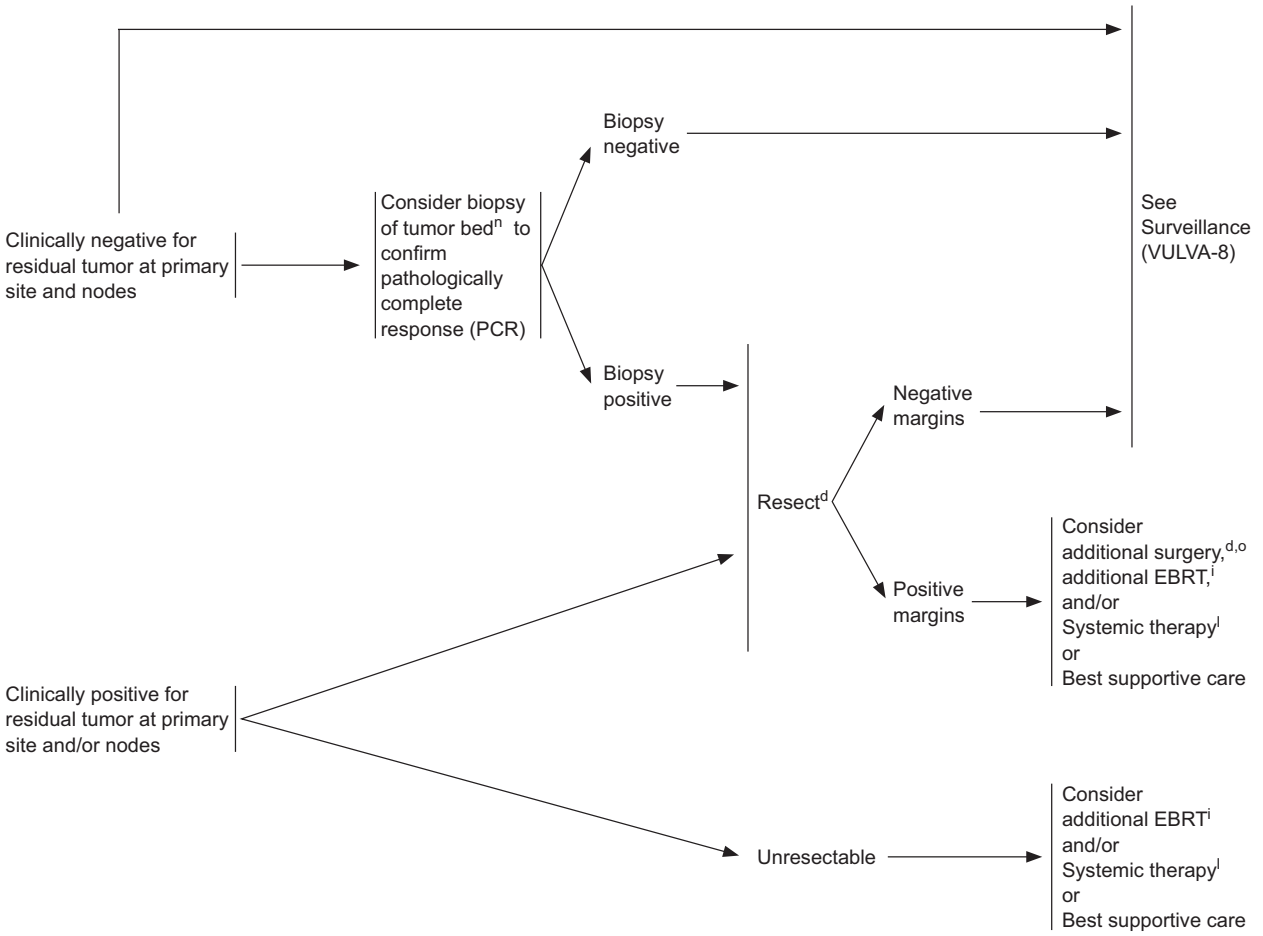


[b]See Principles of Imaging (VULVA-A).
[d]See Principles of Surgery (VULVA-B).
[i]See Principles of Radiation Therapy (VULVA-C).
[l]See Systemic Therapy (VULVA-D).
[m]Larger T2 tumors: >4 cm or with involvement of the urethra, vagina, or anus.

VULVA-5
AND
VULVA-7

EVALUATION OF RESPONSE TO EBRT + CONCURRENT CHEMOTHERAPY

ADDITIONAL TREATMENT

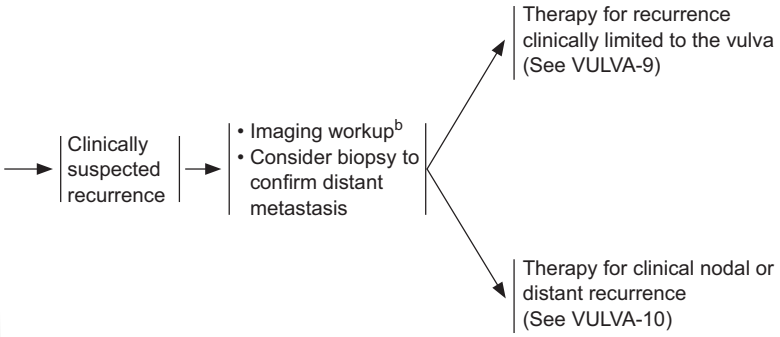


[d]See Principles of Surgery (VULVA-B).
[i]See Principles of Radiation Therapy (VULVA-C).
[l]See Systemic Therapy (VULVA-D).
[n]No sooner than 3 months from completion of treatment.
[o]Consider pelvic exenteration for select cases with a central recurrence.

SURVEILLANCE[p]

- 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[q] as indicated for the detection of lower genital tract neoplasia
- 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
- 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, potential long-term and late effects of treatment (See NCCN Guidelines for Survivorship and NCCN Guidelines for Smoking Cessation, available at NCCN.org)

WORKUP

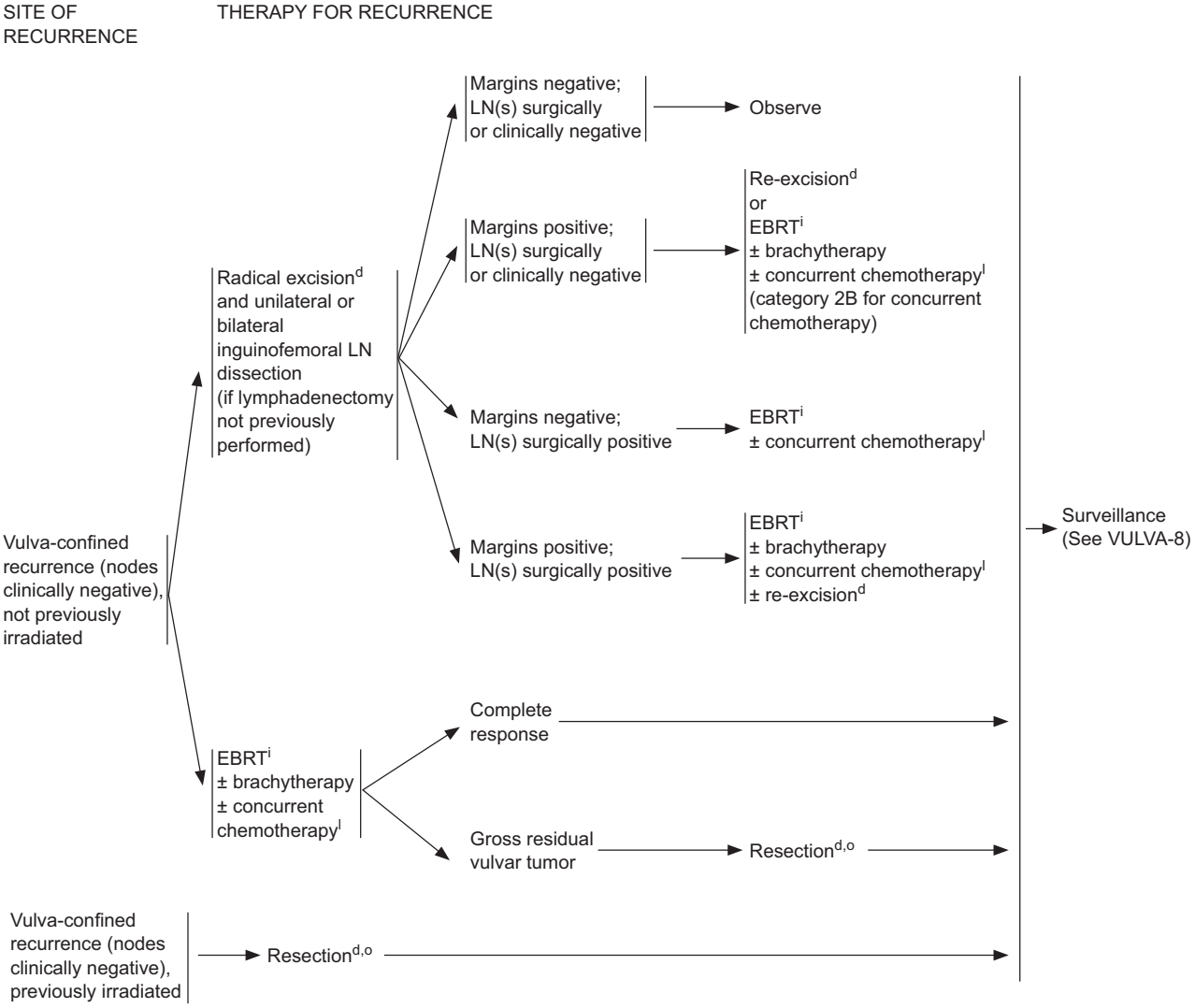


[b]See Principles of Imaging (VULVA-A).

[p]Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 2011;204:466-478.

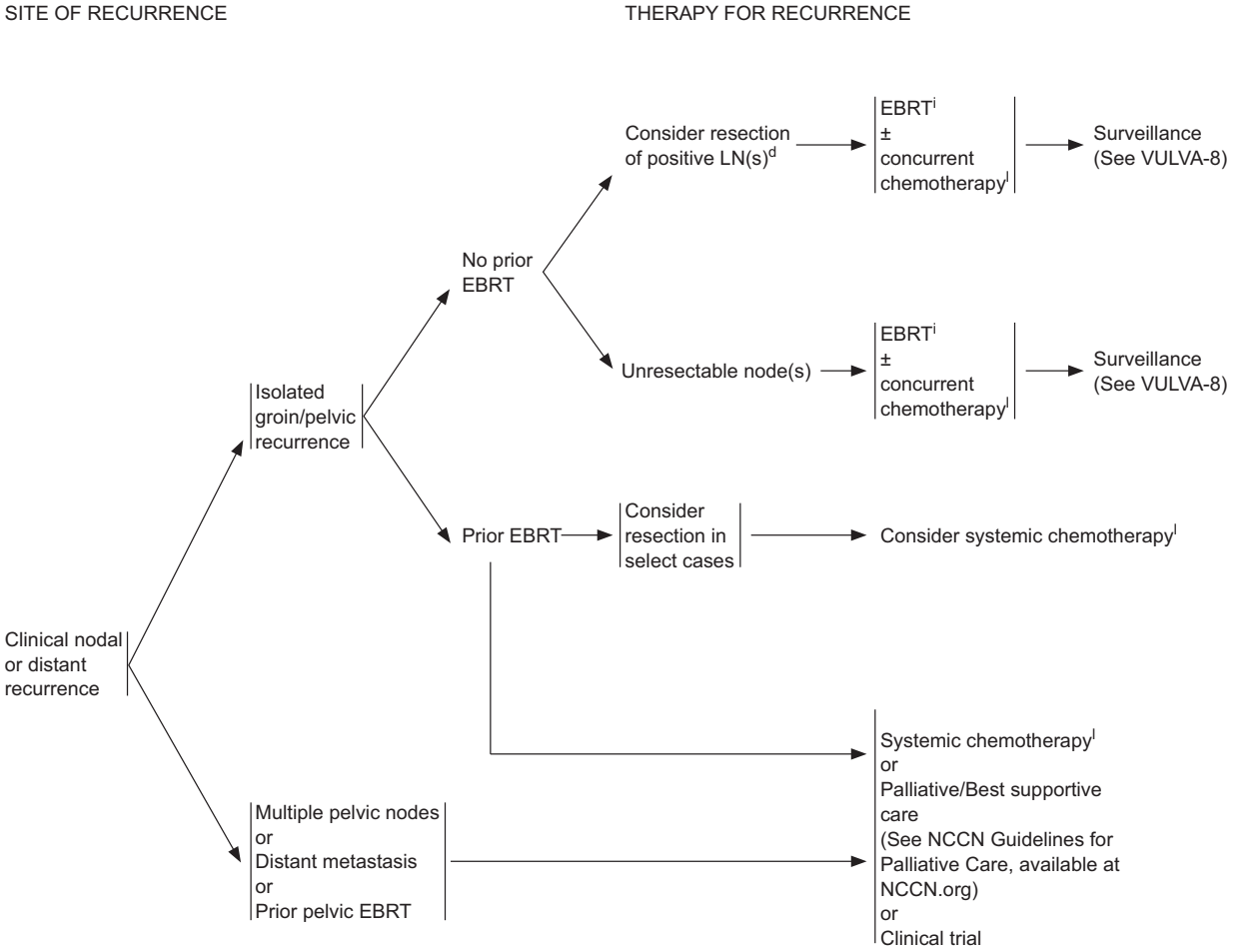
[q]Regular cytology can be considered for detection of lower genital tract dysplasia, although its value in detection of recurrent genital tract cancer is limited. The likelihood of picking up asymptomatic recurrences by cytology alone is low.

Vulvar Cancer, Version 1.2017



[d]See Principles of Surgery (VULVA-B).
[i]See Principles of Radiation Therapy (VULVA-C).
[l]See Systemic Therapy (VULVA-D).
[o]Consider pelvic exenteration for select cases with a central recurrence.

VULVA-9



[d]See Principles of Surgery (VULVA-B).
[i]See Principles of Radiation Therapy (VULVA-C).
[l]See Systemic Therapy (VULVA-D).

PRINCIPLES OF IMAGING*,[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.**
- Consider whole body PET/CT or chest/abdominal/pelvic CT for T2 or larger tumors or if metastasis is suspected.**
- Other initial imaging should be based on symptomatology and clinical concern for metastatic disease.**

Follow-up/Surveillance

- For patients with locally advanced and/or node-positive disease, optional chest/abdominal/pelvic CT every 6–12 months for 2–3 years.
- Whole body PET/CT may be performed if recurrence/metastasis is suspected.
- Other imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease.***

Imaging for Documented Recurrence

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

PRINCIPLES OF IMAGING
(REFERENCES)

[1]Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 2011;204:466-478.

[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.

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[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.

*MRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT.

**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.

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

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 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 (<8 mm from tumor), re-resection may be considered to obtain more adequate margins. Adjuvant local radiation therapy is another alternative.[4] The risk-benefit ratio and morbidity of these approaches must be considered and individualized in each patient.[a]
- 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.[5]

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).[6,7]
- 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.[8]
- 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.[9]
- The current standard involves resection of the vulvar tumor and LNs through separate incisions.[9]
- 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).[10]
- 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-B 3 of 4).[11]
- For a primary vulvar tumor located within 2 cm from or crossing the vulvar midline, a bilateral inguinofemoral lymphadenectomy[11] or SLN biopsy is recommended.
- Some patients are not candidates for lymphadenectomy including those with stage IA disease due to a <1% risk of lymphatic metastases.[11]
- For patients with stage IB-II disease, inguinal lymphadenectomy is recommended due to a risk of >8% of lymphatic metastases.[11]
- A negative unilateral lymphadenectomy is associated with <3% risk of contralateral metastases.[12]
- In the setting of positive LN disease after unilateral lymphadenectomy, contralateral lymphadenectomy[8] 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.[11]
- 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.[13]

[a]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.[2,4]

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 for wound complications and 30%–70% of patients are at risk of lymphedema.[14]
- 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 squamous cell carcinoma of the vulva.[15,16]
- SLN biopsy results in decreased postoperative morbidity without compromising detection of LN metastases.[15,17]
- 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.[15,16]
- 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.[16,18]
- 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.[16]
- Increased sensitivity of SLN detection is observed when both radiocolloid and dye are used.[15,16,17] 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 peri-tumorally 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.

PRINCIPLES OF SURGERY (REFERENCES)

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[9]DiSaia P, Creasman WT, Rich WM. An alternate approach to early cancer of the vulva. Am J Obstet Gynecol 1979;133:825-832.

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[15]Van der Zee, 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.

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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 external beam RT (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.[1,2]
- 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 intensity-modulated radiation therapy (IMRT) as long as care is given to assure adequate dosing and coverage of tissues at risk for tumor involvement.[1,3] Doses range from 50.4 Gy in 1.8 Gy fractions for adjuvant therapy to 59.4–64.8 Gy in 1.8 Gy fractions for unresectable disease. In select cases, large nodes may be boosted to a dose of approximately 70 Gy.
- 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.
- 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.[4]
- 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. 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 wks.

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

- 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 allow 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 is 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.
- Bolus should be used to ensure adequate dosing to superficial target volume.

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 into the vagina. 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 for 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). Planned treatment volume (PTV) expansion is then 7–10 mm.
- Consider use of image-guided IMRT in select cases (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.[5]

VULVA-C
1 OF 3

VULVA-C
2 OF 3

PRINCIPLES OF RADIATION THERAPY
(REFERENCES)

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SYSTEMIC THERAPY[1]

Chemoradiation
- Cisplatin
- 5-FU and cisplatin
- 5-FU and mitomycin-C[2]

Chemotherapy for Advanced, Recurrent/Metastatic Disease
- Cisplatin
- Carboplatin
- Cisplatin/vinorelbine
- Cisplatin/paclitaxel
- Carboplatin/paclitaxel (category 2B)
- Paclitaxel (category 2B)
- Erlotinib (category 2B)

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Text cont. from page 93.

Estimates of the percentage of vulvar cancers attributable to HPV infection range from conservative estimates of 30% to up to 69%.[9–11] However, HPV infection is detected in 80% to 90% of HSIL. Historically, VIN has been diagnosed in younger women (median age, 45–50 years) and vulvar cancers are diagnosed in older women (median age, 65–70 years).[12,13] Because a large majority of HPV-related vulvar cancers are caused by the HPV-16 and -18 strains, vaccination with currently available HPV vaccines may reduce the burden of HPV-related vulvar cancers in the future.[9,12]

Squamous cell vulvar cancers are typically treated with primary surgery, with the potential integration of radiation (RT) and/or chemotherapy based on pathology and extent of disease.[14] Due to the high rates of morbidity with surgical treatment, the field has shifted from radical approaches to more conservative surgery with the addition of RT or chemoradiation.[15] Because the data are limited, trials are ongoing to identify optimal approaches for neoadjuvant and adjuvant therapy, which may include systemic therapy, RT, or chemoradiation.[16–19] For patients with inoperable or extensive disease, trials have examined neoadjuvant chemoradiation to improve operability rates.[17]

By definition, the NCCN Clinical Practice Guidelines in Oncology (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 panel members during the guideline development process. Recommendations in the NCCN Guidelines are category 2A unless otherwise noted.

Diagnosis and Workup

Currently, these NCCN 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 generally be referred to as "vulvar cancer."

These guidelines utilize the FIGO and AJCC TNM staging systems, which closely align for the staging of vulvar cancer. The FIGO system was updated in 2009[20,21]; the 8th edition of the AJCC Cancer Staging Manual was released in 2016.[22] In the updated FIGO system, major changes include the combination of the former stage I and II, subclassification based on the number and size of involved lymph nodes, and shifting away from the focus on bilateral lymph node involvement.[20] The impact of this revised classification system has been examined.[23–25]

The presentation of vulvar cancer can be widely varied. Most vulvar cancers are located in the labia majora, but 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.[12,13,26] Although many cases may be asymptomatic, pruritus and pain/irritation is a common symptom; vulvar bleeding or discharge may also occur. Most patients present with early-stage (ie, localized) disease.[1]

Diagnosis is made via a biopsy of the suspicious areas followed by pathologic review. The College of American Pathologists protocol for vulvar carcinoma is a useful guide (available at: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cp-vulva-16protocol-3200.pdf). This protocol was revised in January 2016, and it reflects recent updates in the AJCC/FIGO staging.

Workup includes history and physical examination, 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.[27–31] Examination under anesthesia with cystoscopy or proctoscopy should be considered as indicated. Appropriate patients should receive smoking cessation counseling and HPV testing.

Prognostic Factors

Historically, en bloc vulvectomy with wide margins was combined with complete inguinofemoral lymphadenectomy to treat vulvar SCC. Although 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 has informed the evolution of surgical staging and primary treatment.[26] 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 and primary tumor size.[32] Lymph node metastasis is considered the most important prognostic factor and determinant of treatment in vulvar cancer,[33,34] and extracapsular extension has been linked to poorer prognosis.[35–38] Additional factors shown to be predictive of recurrence and/or survival include depth of invasion, tumor thickness, and presence of lymphovascular space invasion (LVSI).[12,32,39–42]

These important prognostic data have guided the shift towards more conservative primary tumor resection and regional lymph node management for early-stage disease.[43] The preferred surgical approach evolved towards vulvar conservation with separate incisions for lymph node dissection in patients who were clinically node-negative.[26,44] Current surgical approaches involve tailored primary tumor resection and lymph node 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

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 primary prognostic factor in vulvar cancer survival,[33,46] 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 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.[47,48]

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 exists for recurrence and/or survival.[49–51] Both surgical approaches involve resection of approximately a 1- to 2-cm margin of grossly normal tissue and to the deep fascia or a minimum of 1 cm of tissue depth.

Vulvar cancer is associated with significant risk of local recurrence, and data demonstrate tumor margin status to be a significant prognostic factor.[39,42,52] 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.[53] The goal of primary tumor resection is complete removal with 1- to 2-cm margins. In the setting of close (<8 mm) or positive tumor margins, re-resection to obtain adequate margins or adjuvant local RT are options.[39,54]

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.[55] 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 with or without 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 (ie, superficial to the inguinal ligament, within the proximal femoral triangle, and deep to the cribriform fascia). 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 <1% in patients with stage IA disease,[45] lymphadenectomy is not required for those with T1A and N0 tumors. However, inguinofemoral lymphadenectomy is recommended for patients with stage IB/II disease because the risk of nodal metastasis is estimated at >8% for stage IB tumors.[45] Lymphadenectomy for stage III/IV disease is individualized and integrated with combined modality approaches. For primary vulvar tumors <4 cm in diameter, located ≥2 cm from the vulvar midline, with clinically negative IFLNs, unilateral inguinofemoral lymphadenectomy or SLN biopsy are appropriate.[56,57] 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.[57]

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.[15,58] In a summary of 12 retrospective studies of patients with negative groin lymphadenectomy, groin recurrence rates varied from 0% to 5.8%,[59] suggesting the potential to safely avoid completion lymphadenectomy in patients with negative SLNs. To investigate this approach, several prospective multicenter trials have evaluated the feasibility, safety, validity, and risk of groin recurrences with SLN biopsy in early-stage vulvar cancer.

The safety of SLN biopsy was examined in a multicenter observational study of 403 women with primary vulvar tumors <4 cm. Inguinofemoral lymphadenectomy was omitted if SLNs 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%. Short- and long-term morbidity was reduced if the SLN only was removed compared with SLN removal followed by full groin dissection.[59]

The GROINSS-V observational study was also performed in this cohort, examining 135 of 403 patients with positive SLNs (33%). Investigators examined the relationship between size of SLN metastasis and risk of non-SLN disease among 115 patients who underwent inguinofemoral lymphadenectomy after detection of positive SLNs. 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. Disease-specific survival (DSS) was worse among those with SLN metastases >2 mm versus ≤2 mm (69.5% vs 94.4%; P=.001).[60] Patients undergoing SLN biopsy reported less treatment-related morbidity compared with those undergoing IFLN dissection; however, patient-reported quality of life did not differ significantly between groups.[61]

Long-term follow-up of the GROINSS-V cohort compared outcomes of SLN-positive patients who underwent IFLN dissection with SLN-negative patients (no IFLN dissection). At a median follow-up of 105 months, the data revealed a 5- and 10-year recurrence rate of 24.6% and 36.4% for SLN-negative patients, respectively, and 33.2% and 46.4% for patients with a positive SLN, respectively (P=.03). DSS at 10 years was 91% in the SLN-negative group and 65% in the SLN-positive group (P<.0001).[62]

In GOG 173, 452 women (with vulva-confined primary tumors 2–6 cm, ≥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).[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%, respectively.[64]

The ongoing GROINSS-V-II/GOG 270 study (ClinicalTrials.gov identifier: NCT01500512) is comparing RT of the groin to 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 low groin recurrences with this surgical approach in vulvar cancer.[59,60,63]

Candidates for SLN biopsy should have clinically/radiologically negative groin nodes, unifocal primary tumor <4 cm, and no history of previous vulvar surgery.[60,64] 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.[63,64] The NCCN Vulvar Cancer 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 may be warranted. Additionally, surgical evaluation or treatment of the contralateral groin is indicated.

Primary Treatment

For the purposes of primary treatment, these NCCN Guidelines provide treatment recommendations by clinical stage, separating patients into those with early-stage (stage I/II), locally advanced (stage III/IVA), and distant metastatic disease (stage IVB, beyond the pelvis). 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 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 and must have disease beyond the pelvis.

Early-Stage Disease

After careful clinical evaluation and staging, standard primary treatment for earlystage vulvar SCC is conservative individualized tumor excision with IFLN evaluation.[44,50,65–68] Clinicians should strive for primary tumor resection with oncologically appropriate margins of 1 to 2 cm if feasible.[39,42,52,54] See "Primary Tumor Resection" and "Lymph Node Evaluation" (page 109). 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.[50,51]

Surgical dissection and RT have been evaluated for treatment of the groin in early-stage disease. Limited data suggest that primary groin RT results in less morbidity than surgical dissection.[14] However, surgical treatment of the groin has been associated with lower groin recurrence rates, therefore, remaining the preferred approach.[69] Primary RT may have some benefit for those unable to undergo surgery.[70,71]

Panel Recommendations: For T1 tumors with ≤1 mm depth of invasion (pT1A), the NCCN Guidelines 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.[45,66,72–75] Patients should be observed following resection. If surgical pathology reveals >1-mm invasion, additional surgery may be indicated.

For patients with T1 or smaller T2 tumors with a depth of invasion >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.[56,57,72] Groin evaluation can be performed through SLN biopsy or ipsilateral IFLN dissection. Dissection should be performed if no SLNs 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.[50,57,72] Groin dissection is required on sides for which SLNs 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.[26,76–78] Additionally, complete resection of locally advanced disease may be complicated by tumor fixed to vital organs or vessels, rendering the disease unresectable.[79] A shift to multimodality treatment was explored to improve organ preservation and reduce surgical treatment morbidity.[80] Preoperative RT was shown in some earlier studies to result in tumor debulking and reduce the extent of surgery required for locally advanced disease.[79,81–84] Subsequently, borrowing on experi-

ence from advanced cervical and anal cancers, chemotherapy typically has been combined added as a "radiosensitizer" when RT is delivered to 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 after chemoradiation. After chemoradiation, at least partial tumor responses were noted among a majority in these cohorts,[85–89] with several studies revealing complete tumor responses among >60% of the cohort.[90–94] Overall survival (OS) after primary chemoradiation was superior to OS after primary RT in a series of 54 patients with locally advanced disease.[95]

In GOG 101, preoperative chemoradiation was examined in 73 patients with stage III/IV disease.[87] The study investigated whether chemoradiation allowed for less radical surgery in patients with T3 tumors and avoidance of pelvic exenteration in those with T4 tumors. Only 3% of patients (2/71) had residual unresectable disease after 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.[96] Subsequent surgery was performed on 38 patients with resectable disease after chemoradiation with cisplatin/5-FU. Local control of nodal disease was achieved in 36 of 37 patients and for the primary tumor in 29 of 38 patients. More recently, GOG 205 examined the feasibility of surgery after chemoradiation with cisplatin in 58 patients with T3/T4 tumors that were initially unresectable by radical vulvectomy.[97] 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 rates have led many to believe that surgery can be avoided in patients with locally advanced tumors who achieve clinical complete responses.

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.[18] 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 nonrandomized 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.[17]

The combination regimen used for radiosensitization was most commonly cisplatin/5-FU,[87,88,90,92,93] but also included 5-FU/mitomycin C[86,89,94] or single-agent therapy.[91,97] The selection of radiosensitizing chemotherapy is often based on an extrapolation of findings from cervical, anal, or head and neck cancer.

Panel Recommendations: Patients with larger T2 or T3 tumors should undergo radiologic imaging if it was 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 positive IFLNs are found on 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 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, 5-FU/cisplatin, and 5-FU/mitomycin-C.[16,98]

Metastasis Beyond the Pelvis

Data on systemic treatments for vulvar SCC with distant metastasis are extremely limited.[99–101] Treat-

ment regimens are often extrapolated from agents that are active against advanced cervical cancer. See "Systemic Therapy for Recurrent/Metastatic Disease" (page 116) for information regarding specific regimens.

Panel Recommendations: Primary treatment options for extra-pelvic metastatic disease include EBRT for control of locoregional disease and symptom control, and/or chemotherapy. Best supportive care is also an alternative in this setting. Agents recommended by the panel for treating advanced recurrent/metastatic disease include cisplatin, carboplatin, paclitaxel (category 2B), and erlotinib (category 2B) as single agents and cisplatin/vinorelbine, cisplatin/paclitaxel, and carboplatin/paclitaxel (category 2B).[16]

Adjuvant Therapy

Because of 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 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.[102] As previously emphasized, it is crucial to prevent metachronous groin relapses, because these often prove refractory to secondary management and are often ultimately fatal.

Early randomized trial data on adjuvant RT was published from GOG 37, which enrolled 114 patients with groin node-positive vulvar cancer after radical vulvectomy and bilateral inguinofemoral lymphadenectomy.[103,104] Patients were randomized to receive pelvic node dissection or adjuvant RT to the groin/pelvis. In the adjuvant RT group, 2- and 6-year survival was superior, 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 those receiving pelvic node resection compared with pelvic/groin RT (51% vs 29%; hazard ratio [HR], 0.49; *P*=.015).[104]

There are conflicting data on the benefit of adjuvant RT in patients with a single positive lymph node. Some studies of patients with a single positive lymph node have reported no benefit to adjuvant RT.[105,106] 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.[107] 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, respectively. The number of involved nodes negatively impacted prognosis in patients receiving no adjuvant RT; however, among patients receiving adjuvant RT to the groin/pelvis, the number of metastatic nodes did not harm prognosis.[108]

A large multicenter retrospective study reported significant survival benefits in node-positive patients receiving adjuvant RT or chemoradiation (3-year progression-free survival [PFS]: 39.6% vs 25.9%; *P*=.004; 3-year OS: 57.7% vs 51.4%; *P*=.17).[106] RT coverage most commonly included the groin and pelvis with or without coverage of the vulva, with a smaller subset receiving coverage to the groin with or without vulvar coverage. Again, the benefits of adjuvant RT were the most clear for patients with ≥2 positive lymph nodes. When adjuvant RT is delivered to the lymph nodes, care should be used to avoid excessive blocking of the central pelvic structures.[109]

Recent examination of data from the National Cancer Database supported the addition of chemotherapy to RT in the adjuvant setting. Among 1,797 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 vs 29.7 months; HR, 0.62; 95% CI, 0.48–0.79; *P*<.001).[110] 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 women (HR, 0.71; 95% CI, 0.57–0.88; *P*=.002) along with a trend toward improved cause-specific survival (HR, 0.79; 95% CI, 0.59–1.05; *P*=.11).[111] Parameters for RT delivery were important among this cohort; 3-year OS and cause-specific survival were significantly improved in patients who received ≥20 fractions (3-year OS: 34% vs 26%; *P*=.008, and 3-year cause-specific survival: 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.[112] 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 a lower risk of recurrence in patients receiving doses of ≥56 Gy compared with those receiving ≤50.4 Gy.[53]

Panel Recommendations: For patients with early-stage disease (T1) and a depth of invasion ≤1 mm (pT1a), observation is appropriate after 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.[59,113–116] Adjuvant therapy is warranted if the SLN or IFLNs contain metastases. Adjuvant therapy for patients with SLN involvement includes: (1) RT (category 1) 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 ≥2 positive IFLNS or a single IFLN with >2-mm metastasis.[103,106]

In additional to nodal status, a number of primary tumor risk factors may influence adjuvant therapy decisions, which include LVSI, close or positive tumor margins, tumor size, depth of invasion, and/or diffuse/spray pattern of invasion. Observation is reasonable in the setting of negative primary tumor margins with no additional risk factors. Treatment should be individualized for patients with primary tumor margins that are positive for noninvasive disease (eg, HSIL). 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.[112] Patients with oncologically appropriate margins after re-excision may be candidates for observation unless additional risk factors warrant adjuvant EBRT. For those 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 NCCN 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 pathologic complete response. 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 year, although recurrences beyond 5 years have been observed in a significant subset of patients.[117] Accordingly, long-term follow-up is indicated. Definitive data on an optimal surveillance strategy is lacking.[118] However, the panel concurs with the updated recommendations from the Society of Gynecologic Oncology for posttreatment surveillance,[119] which 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 VULVA-8, page 100). 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, 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 (available at NCCN.org). Smoking cessation and abstinence should be encouraged, see the NCCN Guidelines for Smoking Cessation (available at NCCN.org).

Sexual dysfunction and low body image is unfortunately common among women who have undergone vulvectomy and/or RT of the groin/pelvis.[15,120,121] Patients who have 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 the use of vaginal moisturizers/lubricants (eg, estrogen creams, nonhormonal 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 the completion of RT and can be performed indefinitely (https://www.mskcc.org/cancer-care/patient-education/improving-your-vaginal-health-after-radiation-therapy).

If persistent or recurrent disease is suspected, patients should be evaluated using additional imaging studies and biopsy as outlined in the following section.

Treatment for Recurrent Disease

A multicenter case series evaluated the rates and patterns of recurrence among 502 patients, of whom 187 (37%) developed recurrent vulvar SCC. More than 50% of recurrences were vulvar (53.4%), followed by inguinal (18.7%), multisite (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.[34] Although localized vulvar recurrences can be successfully addressed with subsequent surgery, some studies have suggested a 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.[122] Treatment approaches and patient outcomes depend on site and extent of recurrent disease.[122,123] Isolated local recurrences can often be treated successfully with radical local excision,[34,124] and RT with or without chemotherapy provided some degree of DFS in several studies.[83,84] A retrospective review of patients with locoregional recurrences that were managed with chemoradiation, neoadjuvant chemotherapy, or RT alone showed 5-year DFS and OS rates of approximately 20%; however, those with a single-site recurrence and lesions ≤3 cm who received an RT dose ≥64.8 Gy remained disease-free at 5 years.[125] Conversely, another series noted a decline in survival for those with nodal metastases, tumors >3 cm, or high-grade lesions.[126] For central/large recurrences, pelvic exenteration has been shown to prolong survival when performed on carefully selected patients.[76,77,127] Regardless of treatment approach, prognosis for nodal recurrences was very poor.[124,126,128,129]

Panel Recommendations

If recurrence is suspected, the NCCN Vulvar Cancer Panel recommends workup for metastatic disease with imaging studies. Biopsy can be considered to confirm distant metastasis. Treatment recommendations for recurrent disease are outlined according to the 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 with unilateral or bilateral IFLN dissection if lymphadenectomy was not previously performed. Pelvic exenteration can be considered for select cases with a central recurrence. Additional therapy is indicated by margin status and nodal status. Observa-

tion 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 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: Chemotherapy, palliative/best supportive care, or clinical trial enrollment is recommended for patients experiencing recurrence who received prior pelvic EBRT and for those 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 resection of positive nodes followed by EBRT with or without concurrent chemotherapy should be considered. 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 chemotherapy 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. An overview of systemic therapies used to treat vulvar SCC is available in the article by Reade et al[16]; recommended systemic therapy agents are listed on VULVA-D, page 107.

Cisplatin is a commonly employed radiosensitizing agent in locally advanced vulvar cancer, and is recommended for single-agent or combination chemotherapy for the treatment of metastatic disease.[79,130] 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.[131]

Carboplatin (category 2A) is an alternative platinum agent active in metastatic cervical cancer that can be used as a single agent or in combination with paclitaxel (category 2B). A small series of 6 patients with advanced or recurrent/metastatic vulvar cancer noted limited clinical benefit of the combination regimen[99]; however, it has been included in these NCCN Guidelines based on data from patients with advanced or recurrent/metastatic cervical cancer.[132]

Paclitaxel (category 2B) was modestly active in a phase II trial of 31 women with advanced recurrent/metastatic vulvar cancer, and generated a response rate of 14% and PFS of 2.6 months.[100]

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.[101]

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Individual Disclosures for the NCCN Vulvar Cancer Panel

Panel Member	Clinical Research Support/ Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Nadeem R. Abu-Rustum, MD	None	None	None	2/16/16
Susana M. Campos, MD, MPH, MS	None	Genentech, Inc.	Merck & Co., Inc.	3/21/16
Kathleen R. Cho, MD	None	Resonant Therapeutics, Inc.	None	3/8/16
Hye Sook Chon, MD	None	None	None	9/15/16
Christina Chu, MD	None	None	None	7/14/16
David Cohn, MD[a]	None	Oncology Analytics; and Up To Date	None	4/20/16
Marta Ann Crispens, MD	AstraZeneca Pharmaceuticals LP; and Janssen Pharmaceutica Products, LP	None	None	9/17/16
Don S. Dizon, MD[a]	None	None	None	2/22/16
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Susan Higgins, MD, MS	None	None	None	4/21/16
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Emily Wyse	None	None	None	9/21/16
Catheryn M. Yashar, MD	None	Cianna Medical; and MicroChips	Varian Medical Systems, Inc.	2/16/16

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty conflict(s):
David Cohn, MD: Society of Gynecologic Oncology
Don S. Dizon, MD: American Journal of Clinical Oncology, ASCO, and UpToDate
Fidel A. Valea, MD: UpToDate