Vulvar Cancer, Version 3.2024

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ABSTRACT

Vulvar cancer is annually diagnosed in an estimated 6,470 individuals and the vast majority are histologically squamous cell carcinomas. Vulvar cancer accounts for 5% to 8% of gynecologic malignancies. Known risk factors for vulvar cancer include increasing age, infection with human papillomavirus, cigarette smoking, inflammatory conditions affecting the vulva, and immunodeficiency. Most vulvar neoplasias are diagnosed at early stages. Rarer histologies exist and include melanoma, extramammary Paget's disease, Bartholin gland adenocarcinoma, verrucous carcinoma, basal cell carcinoma, and sarcoma. This manuscript discusses recommendations outlined in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for treatments, surveillance, systemic therapy options, and gynecologic survivorship.

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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 of any patient with cancer 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 evidence and 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 representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

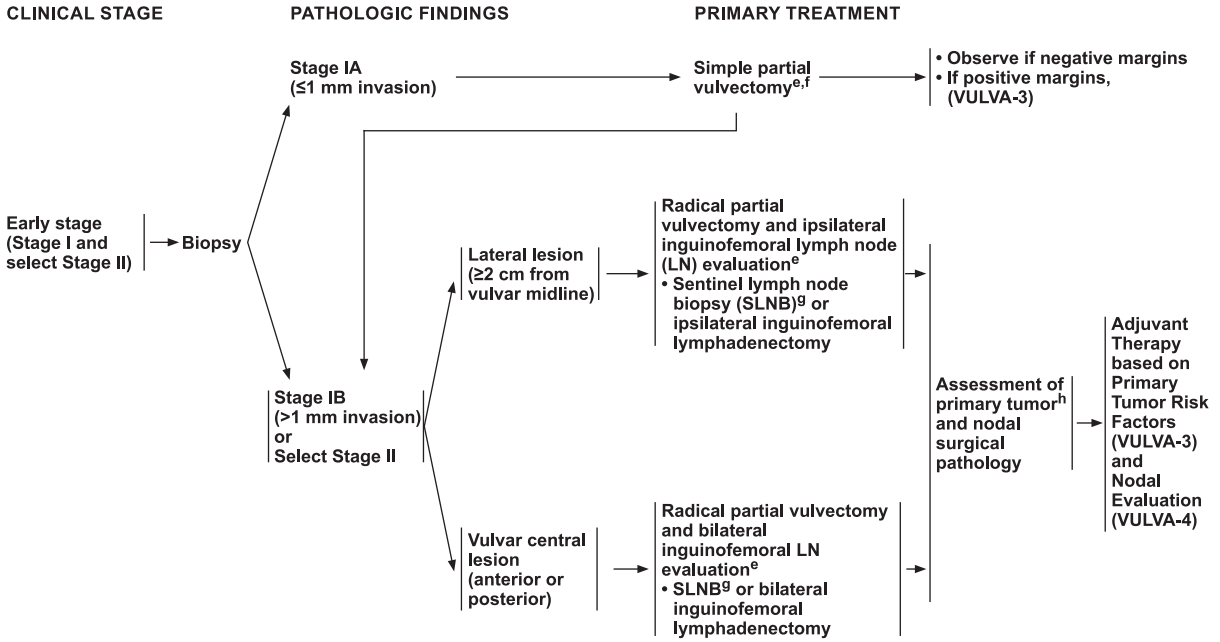
The complete NCCN Guidelines for Vulvar Cancer are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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 135. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



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

*Available online, in these guidelines, at NCCN.org.

VULVA-2

Primary Treatment

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

Early-Stage Disease

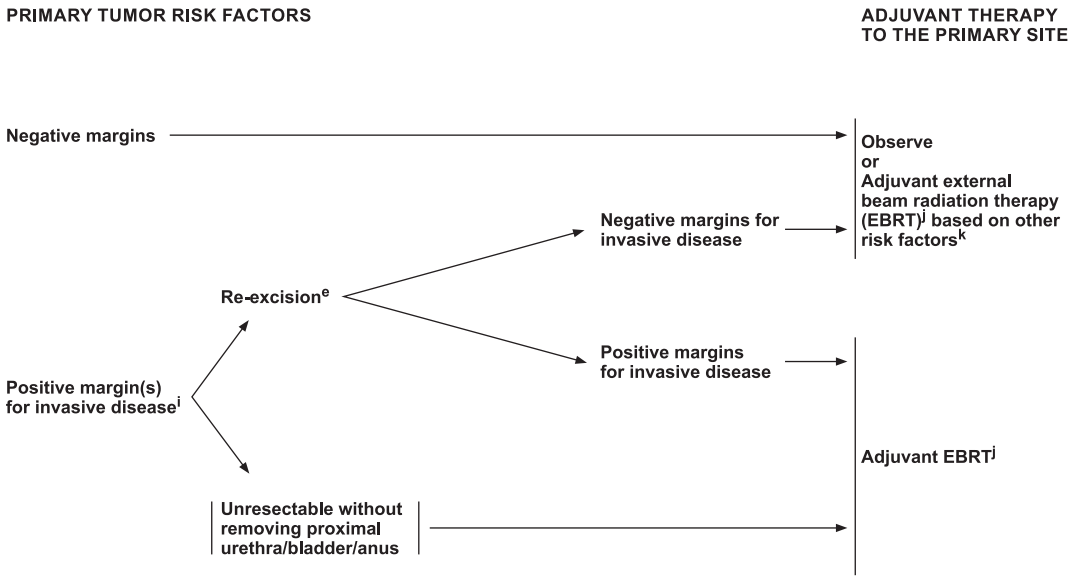
After careful clinical evaluation and staging, the standard primary treatment of early-stage vulvar cancer is conservative, individualized tumor excision with inguinofemoral lymph node (IFLN) evaluation.[1–6] Clinicians should strive for primary tumor resection with oncologically appropriate margins of 1 to 2 cm if feasible.[7–10] See "Primary Tumor Resection" and "Lymph Node Evaluation" sections (available online in this discussion at NCCN.org). Although no prospective data are available comparing radical local incision to radical vulvectomy, existing data from retrospective analyses do not demonstrate a difference in recurrence or survival outcomes.[2,11]

Surgical dissection and radiation therapy (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.[12] However, surgical treatment of the groin (followed by tailored adjuvant RT if lymph node [LN]-positive) has been associated with lower groin recurrence rates and remains the preferred approach.[13] Primary radiation may have some benefit for those unable to undergo surgery.[14,15]

Panel Recommendations

For stage I tumors with ≤1-mm depth of invasion, the panel recommends simple partial vulvectomy; IFLN evaluation is not required due to the low risk of LN metastasis in these patients.[4,16–20] Patients should be observed after resection. If surgical pathology reveals >1-mm invasion, additional surgery may be indicated.

In treatment of patients with stage IB (>1-mm invasion) or select stage II tumors, primary treatment is dictated by tumor location. Patients with lateralized lesions located ≥2 cm from the vulvar midline should undergo radical partial vulvectomy accompanied by ipsilateral IFLN evaluation.[16,21,22] IF node evaluation can be performed through sentinel LN (SLN) biopsy or ipsilateral IF lymphadenectomy; the latter should be performed if no SLN(s) is/are detected. Adjuvant therapy is informed by primary tumor risk factors and nodal surgical pathology. Patients with anterior or posterior central vulvar lesions should undergo radical partial vulvectomy accompanied by bilateral



Surveillance (VULVA-8)

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

*Available online, in these guidelines, at NCCN.org.

VULVA-3

IF node evaluation consisting of SLN biopsy or bilateral IF lymphadenectomy.[2,16,21] IF lymphadenectomy is required on side(s) for which sentinel nodes are not detected. Adjuvant therapy is informed by primary tumor risk factors and nodal surgical pathology. For lateralized and near midline tumors with unilateral SLN metastasis, unilateral groin treatment by either IF lymphadenectomy or RT is acceptable. For midline tumors with unilateral SLN metastasis, unilateral groin treatment can be performed if the contralateral groin has negative sentinel node or negative IF lymphadenectomy.[21,23]

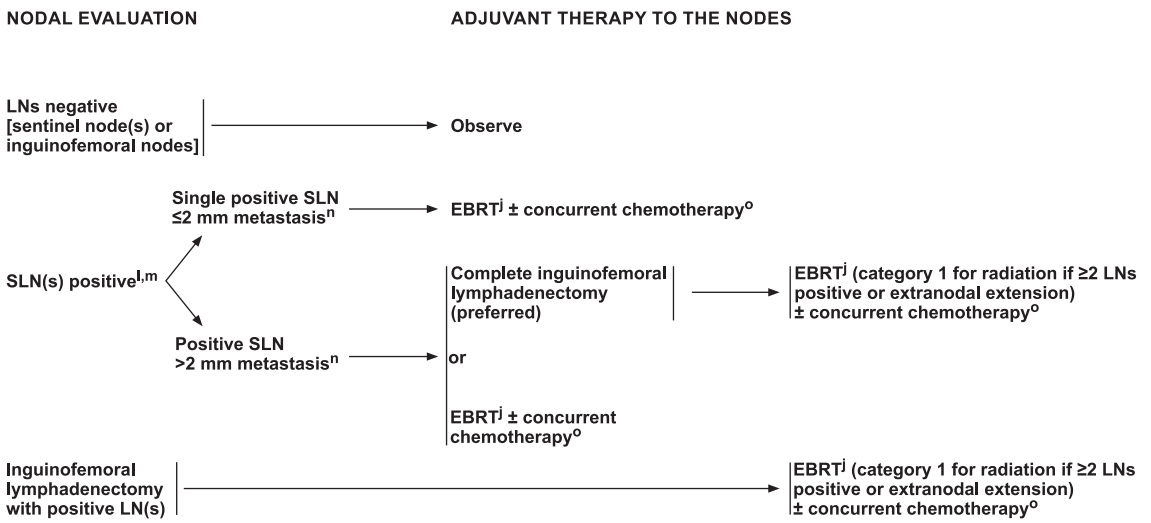
Locally Advanced Disease

Historically, locally advanced vulvar cancers were treated primarily with radical surgeries such as en bloc radical vulvectomy with bilateral IF lymphadenectomy or pelvic exenteration. These surgeries resulted in some cures but also led to significant postoperative complications, loss of function, and reduced quality of life.[24–27] Additionally, complete resection of locally advanced disease may be complicated by tumor fixed to vital organs or vessels, rendering the disease unresectable.[28] A shift to multimodality treatment was explored to improve organ preservation and reduce surgical treatment morbidity.[29] Preoperative RT was shown in some earlier studies to result in tumor debulking and reduce the extent of surgery required for locally advanced disease.[28,30–33] 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 after chemoradiation. Following chemoradiation, at least partial tumor responses were noted among a wide majority of the patients in these cohorts,[34–38] with several studies revealing complete tumor responses among more than 60% of the cohort.[39–43]

Primary chemoradiation may confer a survival benefit over primary RT in vulvar cancer. Overall survival (OS) after primary chemoradiation was superior to OS after primary RT in a series of 54 patients with locally advanced disease.[44] A similar survival benefit was reported in a study using National Cancer Database (NCDB) data from patients who were not candidates for surgery, comparing



[j] Principles of Radiation Therapy (VULVA-D*).
[l] If ipsilateral groin is positive, the contralateral groin should be evaluated. In select cases of a single, small-volume, unilateral, positive inguinal node with a well-lateralized small primary tumor and depth of invasion ≤5 mm and with a clinically negative contralateral groin examination, a contralateral inguinofemoral lymphadenectomy or radiation may be omitted. (Gonzalez Bosquet J, et al. Gynecol Oncol 2007;105:742-746.)
[m] Principles of Surgery: Inguinofemoral Sentinel Lymph Node Biopsy (VULVA-C 4 of 6*).
[n] The size of 2 mm is used to inform treatment selection/management and the 5-mm cutoff is used for staging. See Principles of Pathology (VULVA-A*).
[o] Systemic Therapy (VULVA-E).
*Available online, in these guidelines, at NCCN.org.

Surveillance (VULVA-8)

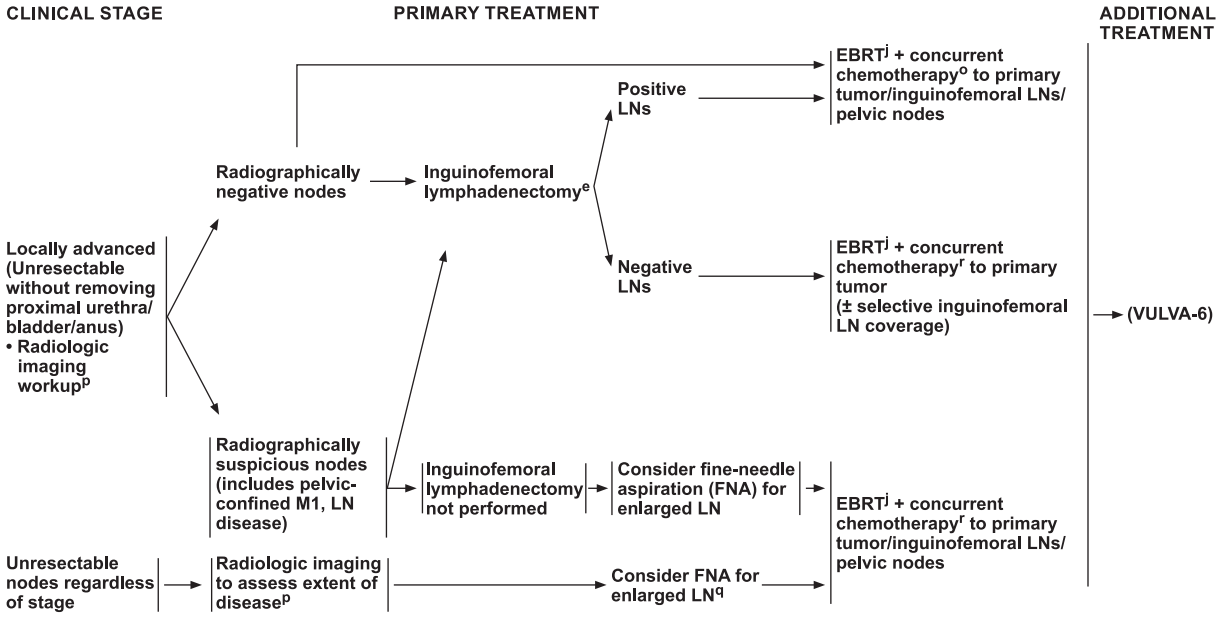
VULVA-4

cohorts who received primary chemoradiation (n=999) or primary RT (n=353). The chemoradiation cohort was younger with more advanced disease based on FIGO staging. Chemoradiation was associated with significantly higher 5-year OS than primary RT (49.9% vs 27.4%; $P<.001$), and multivariate analysis revealed a reduced hazard of death (hazard ratio [HR], 0.76; 95% CI, 0.63–0.91; $P=.003$).[45]

In the GOG 101 study, preoperative chemoradiation was examined in 73 patients with stage III–IV disease.[36] 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 of 71) had residual unresectable disease following chemoradiation, and preservation of urinary and/or gastrointestinal continence was possible in 96% of patients (68 of 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 squamous cell carcinoma (SCC) and N2/N3 nodal involvement.[46] Subsequent surgery was performed on 38 patients with resectable disease after chemoradiation with cisplatin/5-fluorouracil (5-FU). Local control of nodal disease was achieved in 36 of 37 patients and for the primary tumor in 29 of 38 patients. The GOG 205 study examined the feasibility of surgery after chemoradiation with cisplatin in 58 patients with T3–T4 tumors that were initially unresectable by radical vulvectomy.[47] Complete clinical response was noted in 64% of patients (37 of 58), with pathologic complete response (pCR) in 78% (29 of 34) of patients undergoing surgical biopsy. Of the total population, approximately 50% achieved pCR after chemoradiation therapy. The high pCR rates have led many to believe that surgery can be avoided in patients with locally advanced tumors who experience clinical complete responses.

A phase II, multicenter, prospective trial evaluated treatment feasibility, percentage of locoregional control, survival, and toxicity after locoregional radiotherapy combined with sensitizing chemotherapy with capecitabine in 52 patients with T2–T3 tumors.[48] Of the total patients, 58% had no evidence of disease at a median of 35 months. Progression-free survival (PFS) was 58%, 51%, and 45%, and OS was 76%, 66%, and 52% at 1, 2, and 5 years, respectively. Most acute toxicity of grade 3 or greater reported was related to skin/mucosa (54%) and pain (37%). Late toxicity greater of grade 3 or greater was reported for skin/mucosa (10%), fibrosis (4%), gastrointestinal incontinence (4%) and stress fracture or osteoradionecrosis (4%).



[e] Principles of Surgery (VULVA-C*).
[j] Principles of Radiation Therapy (VULVA-D*).
[o] Systemic Therapy (VULVA-E).
[p] Principles of Imaging (VULVA-B*).
[q] Principles of Pathology (VULVA-A*).
*Available online, in these guidelines, at NCCN.org.

VULVA-5

An analysis of NCDB data (2004–2012) compared outcomes of 2,046 females with locally advanced vulvar cancer who received primary radiation (RT or chemoradiation), or preoperative radiation (RT or chemoradiation) followed by surgery. Patients who underwent surgery after RT/chemoradiation had longer OS than patients who underwent primary RT/chemoradiation without subsequent resection (57.1% vs 41.7% at 3 years, respectively; $P<.001$). However, multivariate analysis revealed a radiation dose-dependent effect, and survival was not significantly worse if the dose exceeded 55 Gy. With sufficient RT dose and concurrent chemotherapy, the primary RT cohort had comparable survival to the group who underwent lower-dose preoperative RT/chemoradiation followed by surgery.[49]

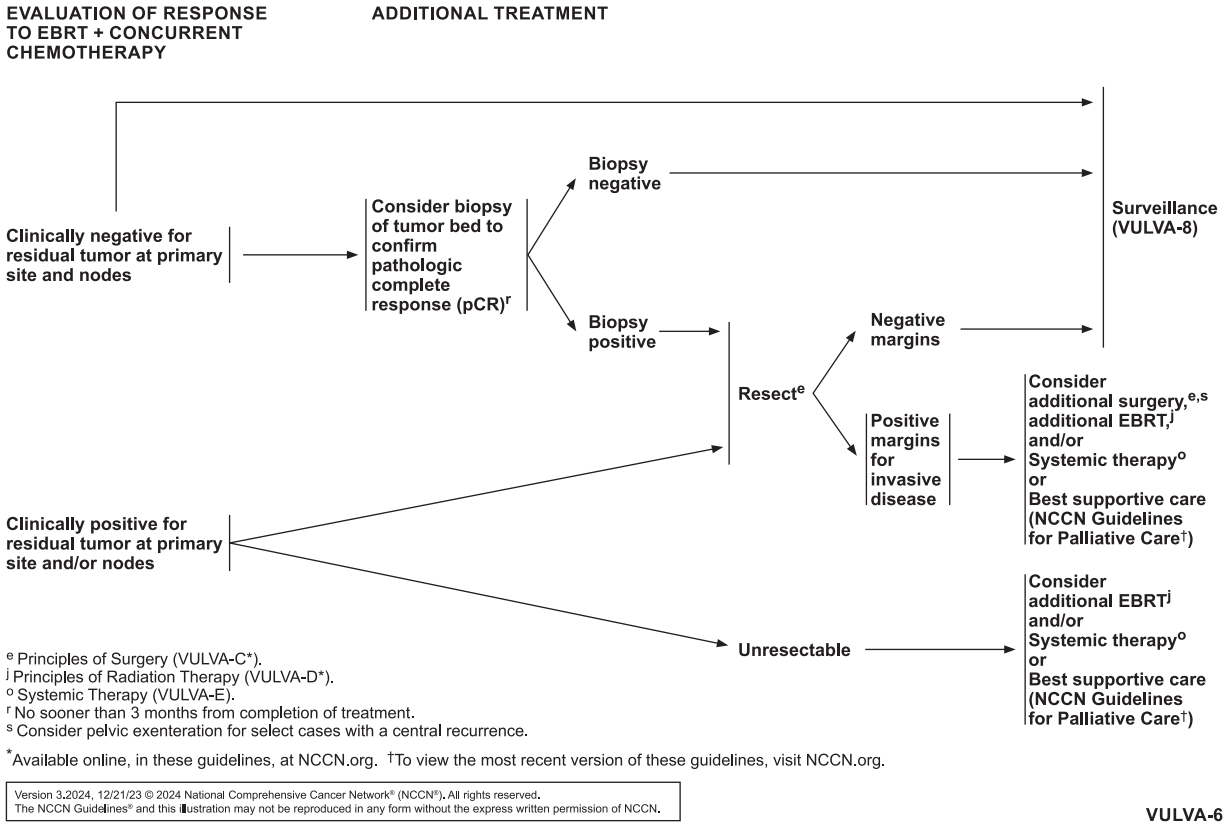
A 2011 Cochrane database review of the existing randomized controlled trial data on 141 females with locally advanced vulvar SCC revealed no difference in OS when comparing primary surgery to primary or neoadjuvant chemoradiation.[50] However, the data did not allow for broad conclusions to be drawn 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.[51]

The combination regimen used for radiosensitization was most commonly cisplatin/fluorouracil,[36,37,39,41,42] but also included fluorouracil/mitomycin C[35,38,43] or single-agent therapy.[40,47] The selection of radiosensitizing chemotherapy is often based on extrapolation of findings from cervical, anal, or head and neck cancer.

Panel Recommendations

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

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



VULVA-6

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

Agents recommended by the panel for chemoradiation include cisplatin (preferred) and carboplatin if the patient is intolerant to cisplatin. The panel also lists cisplatin/fluorouracil under "other recommended regimens."[52]

In addition, if cisplatin or carboplatin are unavailable, the panel has included capecitabine/mitomycin, gemcitabine, and paclitaxel as options that may be considered under the "other recommended regimens" category. These radiosensitizers were added based on a few early-phase studies extrapolated from cervical cancer that have shown their efficacy and tolerability when administered concomitantly with radiation.[53–56]

Metastasis Beyond the Pelvis

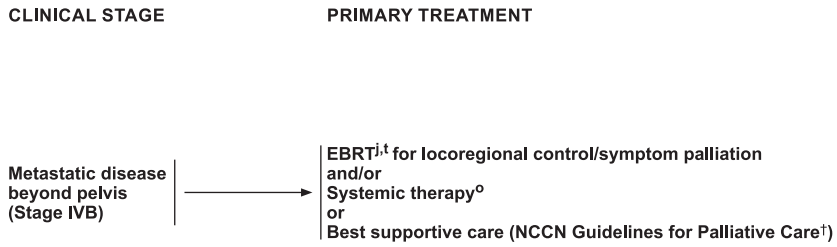
The NCCN panel recommends primary treatment options for extrapelvic metastatic disease including EBRT for control of locoregional disease and symptom palliation, and/or systemic therapy. Best supportive care is also an alternative in this setting. Data on systemic treatments for vulvar cancer with distant metastasis are extremely limited.[57–59] 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 (page 128) for information about specific regimens.

Adjuvant Therapy

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

Adjuvant RT and Chemoradiation

Although it is commonly accepted that LN involvement is a critical prognostic factor in vulvar cancer, the optimal patient selection criteria and adjuvant therapy regimens to address nodal disease continue to be determined.[60] As previously emphasized, it is crucial to prevent metachronous



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

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groin relapses, as these often prove refractory to secondary management and are often ultimately fatal.

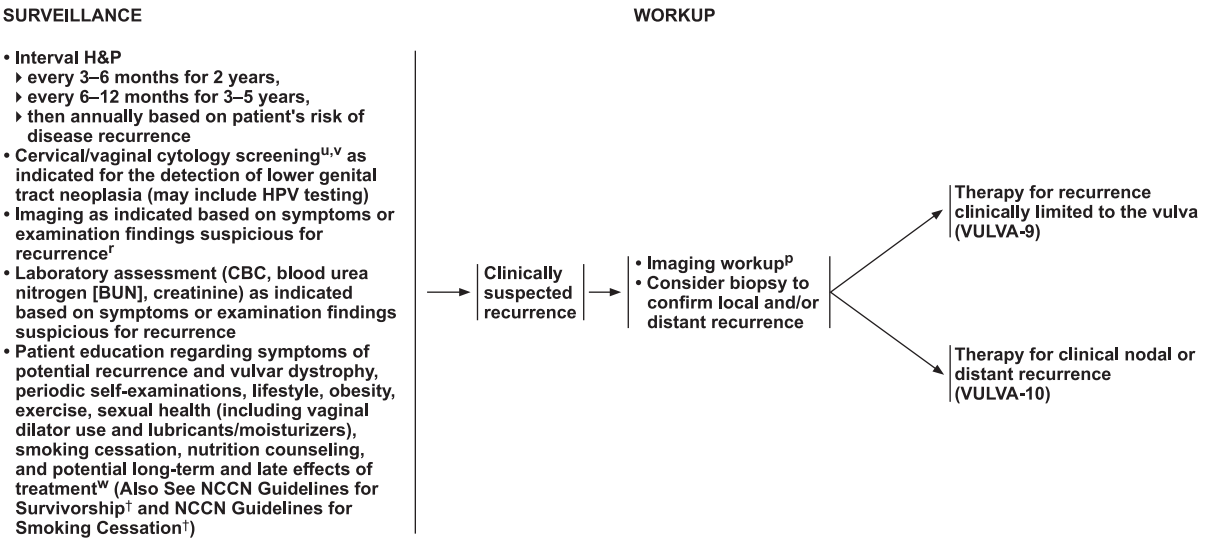
Early randomized trial data on adjuvant RT were published from GOG 37, which enrolled 114 patients with IF node-positive vulvar cancer after radical vulvectomy and bilateral IF lymphadenectomy.[61,62] Patients were randomized to receive pelvic lymphadenectomy or adjuvant RT to the groin/pelvis. Two- and six-year survival were superior in the adjuvant RT group, but the most significant survival benefits were observed among patients with ≥2 positive IF nodes or those with fixed ulcerative IF nodes. Long-term follow-up (median, 74 months) revealed higher rates of disease-related death for the group receiving pelvic node resection compared with pelvic/groin RT (51% vs 29%; HR, 0.49; $P=.015$).[62]

A study using SEER-Medicare–linked data examined outcomes for 444 older patients (aged ≥66 years; median age, 78) with node-positive vulvar cancer who underwent adjuvant RT. Compared with 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 intratreatment break. However, only half of the cohort that received RT met these treatment benchmarks.[63]

Data on the benefit of adjuvant RT in patients with a single positive LN are conflicting. Some studies in patients with a single positive LN have reported no benefit of adjuvant RT in this setting.[64,65] However, examination of SEER data from 208 patients with stage III, single node-positive vulvar SCC revealed significant improvements in 5-year disease-specific survival with the addition of adjuvant RT compared with those receiving no RT.[66] 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 patients with node-negative disease, but 60%, 43%, and 29% in patients with 1, 2, and greater than 2 positive nodes. The number of involved nodes negatively impacted prognosis in patients receiving no adjuvant RT, but among patients receiving adjuvant RT to the groin/pelvis, the number of metastatic nodes did not harm prognosis.[67]

The large, multicenter, retrospective AGO-CaRE-1 study reported significant survival benefits in patients with node-positive disease receiving adjuvant RT or chemoradiation (3-year PFS of 39.6% vs 25.9%, $P=.004$; 3-year OS of 57.7% vs 51.4%, $P=.17$).[65] RT coverage most commonly included the groin and pelvis ± coverage of



[p] Principles of Imaging (VULVA-B*).
[u] Regular cytology can be considered for detection of lower genital tract dysplasia, although its value in detection of recurrent genital tract cancer is limited.
[v] The accuracy of cytology results may be affected in patients who have received pelvic radiation.
[w] Principles of Gynecologic Survivorship (VULVA-F).

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

VULVA-8

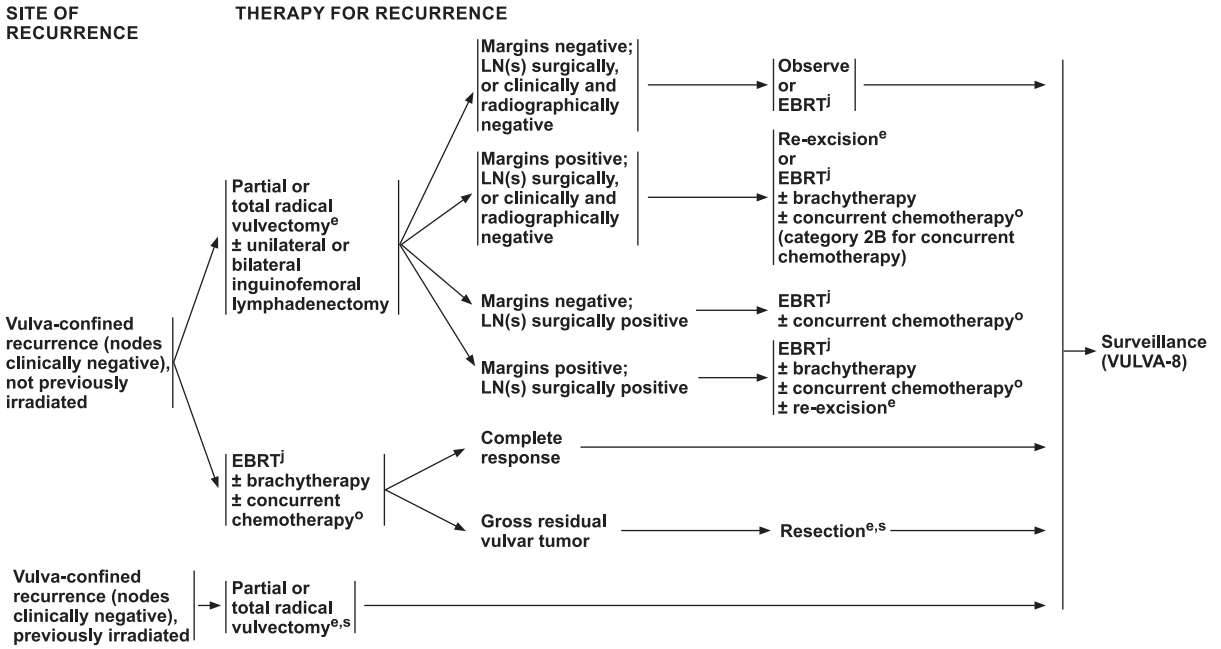
the vulva, with a smaller subset receiving coverage to the groin ± vulvar coverage. Again, the benefits of adjuvant RT were most clear for patients with ≥2 positive LNs.

An examination of data from the NCDB 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; $P<.001$).[68] 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; $P=.11$).[69] Parameters for delivery of RT 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%, $P=.008$; 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.[70] 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.[71]

Panel Recommendations

For patients with early-stage disease (stage I) and a depth of invasion ≤1 mm, observation is appropriate after primary surgery if negative margins are present, and the patient does not have any primary risk factors. Risk factors that may require adjuvant EBRT to the primary site are close tumor margins, lymphovascular space invasion, tumor size, depth of invasion, and pattern of invasion (spray or diffuse). Those with positive margins should undergo re-excision, or if the disease is unresectable without removing proximal urethra/bladder/anus,



[e] Principles of Surgery (VULVA-C*).
[j] Principles of Radiation Therapy (VULVA-D*).
[o] Systemic Therapy (VULVA-E).
[s] Consider pelvic exenteration for select cases with a central recurrence.

*Available online, in these guidelines, at NCCN.org.

VULVA-9

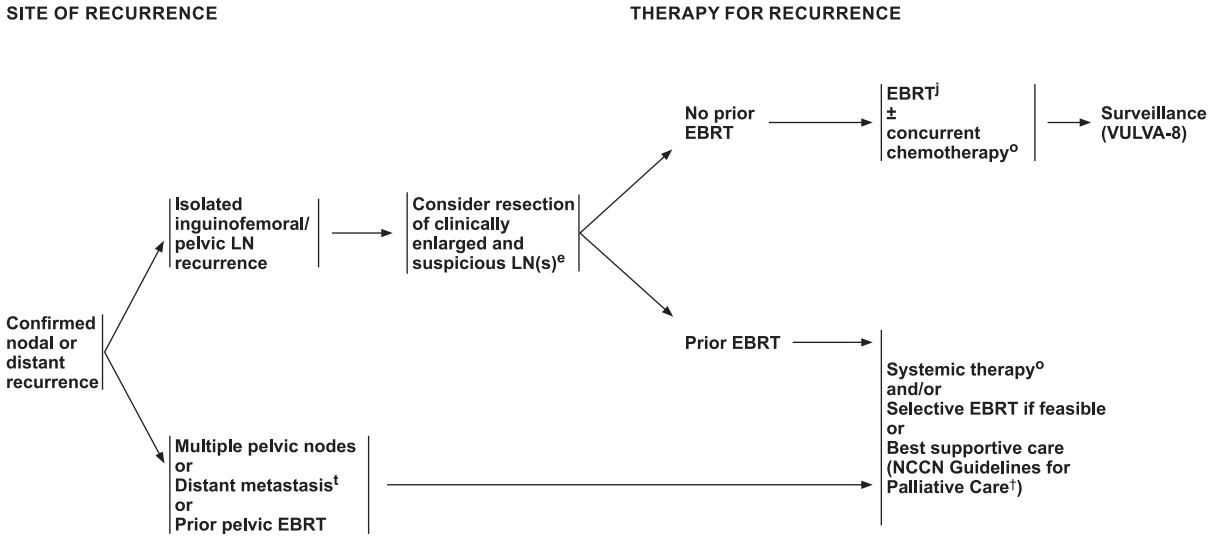
adjuvant EBRT. After re-excision, the panel recommends that patients with negative margins undergo observation or risk factor–dependent EBRT; those with continued positive margins after re-excision should all undergo EBRT.[70]

For patients with stage IB (>1-mm invasion) and stage II disease, surgical evaluation of the groin is indicated in addition to primary site surgery. Nodal status is an important determinant of adjuvant therapy recommendations. For patients with a negative SLN or negative IFLNs, observation can be considered.[72–76] Adjuvant therapy is warranted if the SLN or IFLNs contain metastases. Adjuvant therapy for patients with SLN involvement includes (1) RT ± concurrent chemotherapy; or (2) completion IF lymphadenectomy followed by EBRT ± concurrent chemotherapy. Adjuvant therapy for patients who have positive IFLNs detected during IF lymphadenectomy includes EBRT (category 1) ± concurrent chemotherapy. Chemoradiation is strongly recommended for patients with 2 or more positive IFLNS or a single IFLN with >2-mm metastasis.[61,65] For patients with locally advanced disease, adjuvant therapy decisions should be made based on clinical evaluation of treatment response after EBRT with concurrent chemotherapy (potentially preceded by IF lymphadenectomy). These guidelines provide adjuvant therapy recommendations based on whether patients are clinically negative or positive for residual tumor at the primary site and in the groin. Patients with no clinical evidence of residual tumor after EBRT with concurrent chemotherapy should undergo surveillance. Biopsy of the tumor bed can also be considered to confirm pCR. Patients with residual tumor should be considered for resection. In the case of positive margins on resection, providers should consider additional surgery, additional EBRT, and/or systemic therapy, or best supportive care. For unresectable residual disease, providers should consider additional EBRT and/or systemic therapy, or best supportive care.

Surveillance

Most recurrences of vulvar cancer occur within the first 1 to 2 years, although recurrences beyond 5 years have been observed in a significant subset of patients.[77,78] Accordingly, long-term follow-up is indicated. Definitive data on an optimal surveillance strategy are lacking.[79] However, the panel concurs with the Society of Gynecologic Oncology (SGO) recommendations for posttreatment surveillance.[80]

The recommended surveillance is based on the patient's risk for recurrence and personal preferences.



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

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

VULVA-10

History and physical examination are recommended every 3 to 6 months for 2 years, every 6 to 12 months for another 3 to 5 years, and then annually (see "Surveillance," page 125). Patients with high-risk disease can be assessed more frequently (eg, every 3 months for the first 2 years) than patients with low-risk disease (eg, every 6 months).

Annual cervical/vaginal cytology tests, which may include HPV testing, can be considered as indicated for detection of lower genital tract dysplasia, although its value in detecting recurrent cancers is limited and the likelihood of detecting asymptomatic recurrence is low. In addition, the accuracy of these tests may be affected in patients who have received pelvic radiation because radiotherapy can induce changes in cellular morphology that may result in cytologic misdiagnosis. Imaging (ie, chest/abdomen/pelvis CT, neck/chest/abdomen/pelvis/groin FDG-PET/CT, pelvic MRI) and laboratory testing (ie, CBC count, 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 is periodic self-examination. Patients should also be counseled on healthy lifestyle, obesity, nutrition, exercise, and sexual health (including vaginal dilator use and lubricants/moisturizers). For information on these and other issues related to survivorship (ie, pain/neuropathy, fear of recurrence, depression), see "Gynecologic Survivorship" (page 130) and 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).

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

Treatment of Recurrent Disease

A multicenter case series evaluated the rate and patterns of recurrence among 502 patients, 187 (37%) of whom developed a recurrent vulvar SCC. Just over half 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.[81] Although 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

SYSTEMIC THERAPY[a,1]

Chemoradiation	Advanced or Recurrent/Metastatic Disease	
	First-line Therapy[c]	Second-line or Subsequent Therapy
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant **Other Recommended Regimens** • Cisplatin/fluorouracil • If cisplatin or carboplatin are unavailable:[b] ▸ Capecitabine/mitomycin[2] ▸ Gemcitabine[3] ▸ Paclitaxel[4,5]	**Preferred Regimens** • Cisplatin/paclitaxel/bevacizumab[d] • Cisplatin/paclitaxel • Carboplatin/paclitaxel • Carboplatin/paclitaxel/bevacizumab (category 2B)[d] **Other Recommended Regimens** • Cisplatin • Carboplatin	**Other Recommended Regimens** • Paclitaxel • Cemiplimab[e,6,7] • Erlotinib (category 2B)[8] • Cisplatin/gemcitabine (category 2B) **Useful in Certain Circumstances (Biomarker directed therapy)** • Pembrolizumab[e] (for TMB-high [TMB-H],[f,9] PD-L1–positive,[g] or MSI-high [MSI-H]/MMR deficient [dMMR] tumors[10]) • HPV-related tumors ▸ Nivolumab[e,11] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

Footnotes
[a] Cisplatin, carboplatin, and paclitaxel may cause drug reactions (See NCCN Guidelines for Ovarian Cancer[†]—Management of Drug Reactions [OV-D]).
[b] These agents may be considered when cisplatin and carboplatin are unavailable.
[c] If not used previously, first-line agents can be used as second-line or subsequent therapy as clinically appropriate.
[d] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[e] NCCN Guidelines for Management of Immunotherapy-Related Toxicities[†].
[f] For the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
[g] Recommended for disease progression on or after chemotherapy in patients whose tumors express PD-L1 (combined positive score [CPS] ≥1) as determined by an FDA-approved assay or a validated test performed in a CLIA-certified laboratory.

[†]To view the most recent version of these guidelines, visit NCCN.org.

standard of care exists.[82] Treatment approach and patient outcomes depend on the site and extent of recurrent disease.[82,83] Isolated local recurrences can often be treated successfully with radical local excision,[78,81,84] and RT ± chemotherapy provided some degree of DFS in several studies.[32,33] A retrospective review evaluated patients with locoregional recurrences treated via chemoradiation, neoadjuvant chemotherapy, or RT alone. Five-year DFS and OS were around 20%; however, those with single-site recurrence and lesions ≤3 cm who received RT dose at or above 64.8 Gy remained disease-free at 5 years.[85] Conversely, another series noted decline in survival with the presence of nodal metastases, tumors >3 cm, or high-grade lesions.[86] For central/large recurrences, pelvic exenteration has been shown to prolong survival when performed on carefully selected patients.[25,26,87] Regardless of treatment approach, prognosis for nodal recurrences was very poor.[78,84,86,88,89]

Panel Recommendations

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

Vulva-Confined Recurrence

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

Nonsurgical therapy for recurrence includes EBRT ± brachytherapy and/or concurrent chemotherapy. Resection

SYSTEMIC THERAPY
REFERENCES

[1] Reade CJ, Eiriksson LR, Mackay H. Systemic chemotherapy in squamous cell carcinoma of the vulva: current status and future directions. Gynecol Oncol 2014;132:780-789.
[2] Lorvidhaya V, Chitapanaarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. Int J Radiat Oncol Biol Phys. 2003;55:1226-1232.
[3] Pattaranutaporn P, Thirapakawong C, Chansilpa Y, et al. Phase II study of concurrent gemcitabine and radiotherapy in locally advanced stage IIIB cervical carcinoma. Gynecol Oncol 2001;81:404-407.
[4] Candelaria M, Garcia-Aria A, Cetina L, et al., Radiosensitizers in cervical cancer. Cisplatin and beyond. Radiat Oncol 2006;1:15.
[5] Cerrotta A. Gardan G, Raspagliesi F, et al., Concurrent radiotherapy and weekly paclitaxel for locally advanced or recurrent squamous cell carcinoma of the uterine cervix. A pilot study with intensification of dose. Eur J Gynaecol Oncol 2002;23:115-119.
[6] Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med 2018;379:341-351.
[7] Tewari KS, Monk BJ, Vergote I, et al. Survival with Cemiplimab in Recurrent Cervical Cancer. N Engl J Med 2022;386:544-555.
[8] 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.
[9] Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353-1365.
[10] Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1-10.
[11] Naumann RW, Hollebecque A, Meyer T, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: Results from the Phase I/II CheckMate 358 Trial. J Clin Oncol 2019;37:2825-2834.

can be considered for patients with gross residual tumor. When feasible, partial or total radical vulvectomy is also indicated for patients with vulva-confined recurrence who underwent previous irradiation. After treatment of recurrence, patients should undergo surveillance.

Confirmed Nodal or Distant Recurrence

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

Systemic Therapy for Recurrent/ Metastatic Disease

No standard systemic therapy regimens exist for treating advanced or recurrent/metastatic disease. Several reports provide anecdotal evidence for various regimens, at times extrapolating from regimens with known activity in advanced cervical and anal cancers and other SCCs. Review articles by Reade et al[52] and Mahner et al[82] provide an overview of systemic therapies that have been used to treat vulvar SCC.' Preferred, first-line regimens recommended by the panel for treating advanced, recurrent/metastatic disease include cisplatin/paclitaxel, carboplatin/paclitaxel, and cisplatin/paclitaxel/bevacizumab. Carboplatin/paclitaxel/bevacizumab is included as a category 2B regimen under the preferred, first-line options. Other recommended regimens include single-agents cisplatin and carboplatin.

Cisplatin is a commonly used radiosensitizing agent in locally advanced vulvar cancer, and is recommended for single-agent or combination chemotherapy for treatment of metastatic disease.[28,90] Cisplatin/paclitaxel and cisplatin/paclitaxel/bevacizumab are preferred regimens based on extrapolation of randomized phase III trial data in advanced or recurrent/metastatic cervical cancer.[91,92]

Carboplatin is an alternative platinum agent active in metastatic cervical cancer that can be used as a single agent or in combination. A small series in 6 patients with advanced or recurrent/metastatic vulvar cancer noted limited clinical benefit of the combination regimen[57]; however, it has been included in these guidelines based on data from patients with advanced or recurrent/metastatic cervical cancer that suggest noninferiority to cisplatin.[93,94]

PRINCIPLES OF GYNECOLOGIC SURVIVORSHIP

Physical Effects

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

Psychosocial Effects

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

Clinical Approach

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

Additional Guidance

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

†To view the most recent version of these guidelines, visit NCCN.org.

VULVA-F

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

Single-agent paclitaxel was modestly active in a phase II trial of 31 women with advanced, recurrent/metastatic vulvar cancer, generating a response rate of 14% and PFS of 2.6 months.[58] 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.[59] Cisplatin/gemcitabine is also included as a category 2B option extrapolating from cervical cancer data; however, findings from case reports have been mixed.[95,96]

In the recent NCCN Guidelines update, the panel also included cemiplimab as a second-line or subsequent therapy option under "other recommended regimens." The recommendation of cemiplimab has been extrapolated from its efficacy shown in cervical cancer and in advanced cutaneous SCC. In a phase 2 trial with patients with metastatic cutaneous SCC, a response was observed in 28 of 59 patients.[97] Median follow-up was 7.9 months. The phase III, randomized, Empower-Cervical-1 clinical trial evaluated the efficacy of cemiplimab or investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) in patients with recurrent or metastatic cervical cancer who have progressed on prior therapy. The trial enrolled 608 patients who had previously received one or more lines of systemic therapy for recurrence; they were randomized to either receive cemiplimab or chemotherapy. The median OS and PFS were significantly longer in the cemiplimab arm than in the control arm (12 vs 8.5 months; HR, 0.69; 95% CI, 0.56–0.84; $P<.001$ and 2.8 vs 2.9 months; HR, 0.75; 95% CI, 0.63–0.89; $P<.001$, respectively). Sixteen percent of the patients in the test arm experienced an objective response (95% CI, 12.5–21.1) as compared with 6.3% (95% CI, 3.8–9.6) in the chemotherapy arm.[98]

Biomarker-directed systemic therapies are an emerging class of treatments that may be useful in patients with advanced or recurrent/metastatic cancer. Monoclonal antibodies that function as programmed cell death protein-1 (PD-1) inhibitors are one such example of these treatments. PD-1 functions as an immune checkpoint protein that promotes antitumor T-cell activity. Many tumors, including vulvar cancer, are known to overexpress programmed death ligand-1 (PD-L1), which disrupts PD-1 function. Thus, blocking PD-L1/PD-1 binding restores T-cell–mediated antitumor activity.[99–101] An estimated 10%–50% of vulvar cancers express PD-L1.[102,103]

Pembrolizumab is one such PD-1 inhibitor that may be effective in patients with vulvar cancer. A case study was published of a single patient with recurrent vulvar SCC who was treated with single-agent pembrolizumab, as part of a phase II basket clinical trial to evaluate efficacy and safety,[104] and had 30% reduction in tumor lesions before the treatment was discontinued due to grade 3 mucositis.[105] The single-arm phase II KEYNOTE-158 basket trial (NCT02628067) measured response to pembrolizumab monotherapy in patients with advanced solid tumors that progressed after standard-of-care systemic therapy.[106] Among 101 patients enrolled in the vulvar SCC cohort, median follow-up was 36 months. The overall response rate (ORR) was 10.9% overall, 9.5% in the PD-L1–positive population, and 28.6% among the PD-L1–negative population. Median PFS and OS were 2.1 and 6.2 months, respectively.[107] Pembrolizumab is FDA-approved for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy when tumors express PD-L1 (combined positive score ≥1). The panel has added pembrolizumab as a recommended second-line, useful in certain circumstances option for PD-L1–positive advanced or recurrent/metastatic vulvar cancer.

Monoclonal antibodies targeting the PD-1 pathway may also be effective in tumors that have high tumor mutational burden (TMB-H) or are deficient in mismatch repair (dMMR)/have high levels of microsatellite instability (MSI-H). Of the 71 patients in the KEYNOTE-158 trial with advanced vulvar cancer, 12 had TMB-H tumors. The ORR for TMB-H vulvar cancer was approximately 17%, and the ORR for non–TMB-H disease was 3.4%.[108] The KEYNOTE-158 study authors also analyzed pembrolizumab response in 233 enrolled patients with noncolorectal MSI-H/dMMR tumors, one of whom had vulvar cancer. ORR for the entire cohort was 34.3%. Median PFS was 4.1 months and median OS was 23.5 months.[109] Based on these data, the FDA expanded pembrolizumab's approval for treatment of TMB-H and MSI-H/dMMR tumors that progressed after prior therapy, regardless of tumor type.[110,111] Based on these additional data/FDA approvals, the panel also recommends pembrolizumab as a second-line, useful in certain circumstances option for patients with advanced or recurrent/metastatic vulvar cancer whose tumors are MSI-H/dMMR or TMB-H.

Nivolumab is another PD-1 inhibitor shown to have some efficacy in certain patients with vulvar cancer. The single-arm phase I/II CheckMate 358 trial (ClinicalTrials.gov identifier: NCT02488759) measured response to nivolumab monotherapy in a small cohort of 5 patients with recurrent or metastatic vaginal or vulvar cancer who were HPV-positive or had an unknown HPV status. The 12- and 18-month OS rates for the combined cohort were 40% and 20%, respectively; 6-month PFS was 40%.[112] Based on these data, the panel added nivolumab as a second-line, useful in certain circumstances option for HPV-related advanced or recurrent/metastatic vulvar cancer.

NTRK gene fusions lead to constitutively active tropomyosin receptor kinases (TRKs), which in turn promote development and progression of cancer. Approximately 0.3% of solid tumors express *NTRK* gene fusions, although expression varies widely by cancer type.[113] Entrectinib and larotrectinib are broadly active TRK inhibitors that are effective in patients with a variety of advanced or metastatic *NTRK* fusion–positive solid tumors.[113–115] In a primary analysis, the efficacy and safety of larotrectinib was reported in 55 patients enrolled in 3 clinical studies who had locally advanced or metastatic tumors with *NTRK* gene fusions and had progressed on standard chemotherapy received previously.[114] The 3 clinical trials included a phase I dose-finding study in adults, phase I–II dose-finding study in the pediatric population, and a phase II, single-arm, basket trial. The ORR of larotrectinib in these patients was 75% (95% CI, 61%–85%), with 22% complete response and 53% partial response with median duration of response and PFS not reached at the time. In a long-term follow-up analysis, of 153 patients, 121 patients (79%; 95% CI, 72–85) had an objective response with 16% having a complete response, 63% having a partial response, and 12% having stable disease. The median duration of response was 35.2 months (22.8–not evaluated) and the median PFS was 28.3 months.[116] Similarly, entrectinib showed a durable and clinically meaningful response in 54 patients with advanced/metastatic *NTRK* gene fusion tumors enrolled in 3 phase I–II clinical trials with 57.4% ORR, 10.4-month median duration of response, and 11.2-month median PFS.[113] In a long-term efficacy and safety analysis in 121 patients at median follow-up of 25.8 months, 61% reported complete or partial responses, and median duration of response was 20 months (95% CI, 10.1–19.9). Both larotrectinib and entrectinib are FDA approved for *NTRK* gene fusion solid tumors in patients who have experienced progression after treatment or for whom there is no satisfactory standard therapy. The NCCN Guidelines for Vulvar Cancer recommend larotrectinib and entrectinib as a second-line or subsequent, useful in certain circumstances option for *NTRK* gene fusion–positive tumors and recently changed the category of evidence from category 2B to category 2A.

Gynecologic Survivorship

Treatment of gynecologic cancer typically involves surgery, chemotherapy, hormone therapy, RT, and/or immunotherapy, which may cause acute, short-term, and long-term toxicities. Surgical approaches may be extensive and cause adhesions to form, which in turn may cause pain and contribute to the development of small bowel obstruction, urinary or gastrointestinal complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a

variety of urinary, bowel, and/or sexual effects), and lymphedema.[117,118] Chemotherapy agents vary, though commonly used regimens may pose a significant risk of neurotoxicity, cardiac toxicity, cognitive dysfunction, and the development of hematologic cancers.[119] Long-term estrogen deprivation may cause symptoms such as hot flashes, vaginal dryness, and bone loss. RT may cause long-term complications (eg, fibrosis, stenosis, vulvovaginal atrophy)[120,121] and may predispose patients to subsequent cancers of the skin, subcutaneous tissue, and/or underlying organs that are proximal to the radiation field.[122] Prior pelvic RT may contribute to bone loss and increase the risk of pelvic fractures. Consideration should be given to bone density testing and prophylactic use of bisphosphonates, particularly in patients with osteoporosis. Use of immunotherapy agents in gynecologic cancers is emerging, and to date, long-term effects of these treatments are unknown.[123,124]

Following completion of treatment, all gynecologic cancer survivors should receive regular general medical care that focuses on managing chronic diseases (eg, depression, diabetes, hypertension), monitoring cardiovascular risk factors, receiving recommended vaccinations, and encouraging adoption of a healthy lifestyle (eg, promoting exercise, smoking cessation).[125,126] To assess the late and long-term effects of gynecologic cancers, clinicians should comprehensively document the patient's history, including prior treatment history, and conduct a thorough physical examination and provide any necessary imaging and/or laboratory testing.[126] As most treatments for gynecologic cancers will cause sexual dysfunction, early menopause, and infertility, special attention to the resultant medical and psychosocial implications is needed. All patients, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness.[127] Postradiation use of vaginal dilators and moisturizers is recommended.[120,128] For treatment-related menopause, hormone therapy should be considered. Psychosocial effects may include psychological (eg, depression, anxiety, fear of recurrence, altered body image), financial (eg, return to work, insurance concerns), and interpersonal (eg, relationships, sexuality, intimacy).[126] Patients should be referred to appropriate specialty providers (eg, physical therapy, pelvic floor therapy, sexual therapy, psychotherapy) as needed, based on prior treatment history and assessed risk of developing late effects and/or existing concerns.

Communication and coordination with all clinicians involved in the care of survivors, including primary care clinicians, is critical.[126,129] Providing survivors with a summary of their treatment and recommendations for follow-up is also recommended. To this end, the SGO has developed templates for gynecologic cancer-specific Survivorship Care Plans to aid survivors and their clinicians in summarizing cancer history, treatments received, possible side effects, and recommended follow-up.[130]

References

1. Farias-Eisner R, Cirisano FD, Grouse D, et al. Conservative and individualized surgery for early squamous carcinoma of the vulva: the treatment of choice for stage I and II (T1-2N0-1M0) disease. Gynecol Oncol 1994; 53:55–58.
2. Ansink A, van der Velden J. Surgical interventions for early squamous cell carcinoma of the vulva. Cochrane Database Syst Rev 2000;2000: CD002036.
3. Hacker NF, Berek JS, Lagasse LD, et al. Individualization of treatment for stage I squamous cell vulvar carcinoma. Obstet Gynecol 1984;63: 155–162.
4. Burke TW, Levenback C, Coleman RL, et al. Surgical therapy of T1 and T2 vulvar carcinoma: further experience with radical wide excision and selective inguinal lymphadenectomy. Gynecol Oncol 1995;57:215–220.
5. Hacker NF, van der Velden J. Conservative management of early vulvar cancer. Cancer 1993;71(4 Suppl):1673–1677.
6. Morgan MA, Mikuta JJ. Surgical management of vulvar cancer. Semin Surg Oncol 1999;17:168–172.
7. de Hullu JA, Hollema H, Lolkema S, et al. Vulvar carcinoma. The price of less radical surgery. Cancer 2002;95:2331–2338.
8. Heaps JM, Fu YS, Montz FJ, et al. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol 1990;38:309–314.
9. Rouzier R, Haddad B, Plantier F, et al. Local relapse in patients treated for squamous cell vulvar carcinoma: incidence and prognostic value. Obstet Gynecol 2002;100:1159–1167.
10. Chan JK, Sugiyama V, Pham H, et al. Margin distance and other clinico-pathologic prognostic factors in vulvar carcinoma: a multivariate analysis. Gynecol Oncol 2007;104:636–641.
11. DeSimone CP, Van Ness JS, Cooper AL, et al. The treatment of lateral T1 and T2 squamous cell carcinomas of the vulva confined to the labium majus or minus. Gynecol Oncol 2007;104:390–395.
12. van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. Cochrane Database Syst Rev 2011;2011:CD002224.
13. Stehman FB, Bundy BN, Thomas G, et al. Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys 1992;24:389–396.
14. Hallak S, Ladi L, Sorbe B. Prophylactic inguinal-femoral irradiation as an alternative to primary lymphadenectomy in treatment of vulvar carcinoma. Int J Oncol 2007;31:1077–1085.
15. Petereit DG, Mehta MP, Buchler DA, et al. Inguinofemoral radiation of N0,N1 vulvar cancer may be equivalent to lymphadenectomy if proper radiation technique is used. Int J Radiat Oncol Biol Phys 1993;27: 963–967.
16. Rouzier R, Haddad B, Atallah D, et al. Surgery for vulvar cancer. Clin Obstet Gynecol 2005;48:869–878.
17. Stehman FB, Look KY. Carcinoma of the vulva. Obstet Gynecol 2006; 107:719–733.
18. Magrina JF, Gonzalez-Bosquet J, Weaver AL, et al. Squamous cell carcinoma of the vulva stage IA: long-term results. Gynecol Oncol 2000;76:24–27.
19. Yoder BJ, Ruffomy I, Massoll NA, et al. Stage IA vulvar squamous cell carcinoma: an analysis of tumor invasive characteristics and risk. Am J Surg Pathol 2008;32:765–772.
20. Wilkinson EJ. Superficial invasive carcinoma of the vulva. Clin Obstet Gynecol 1985;28:188–195.
21. Coleman RL, Ali S, Levenback CF, et al. Is bilateral lymphadenectomy for midline squamous carcinoma of the vulva always necessary? An analysis from Gynecologic Oncology Group (GOG) 173. Gynecol Oncol 2013;128:155–159.
22. Woelber L, Eulenburg C, Grimm D, et al. The risk of contralateral nonsentinel metastasis in patients with primary vulvar cancer and unilaterally positive sentinel node. Ann Surg Oncol 2016;23:2508–2514.

23. Van der Kolk WL, Van der Zee AG, Slomovitz BM, et al. Unilateral inguinofemoral lymphadenectomy in patients with early-stage vulvar squamous cell carcinoma and a unilateral metastatic sentinel lymph node is safe. Gynecol Oncol 2022;167:3–10.
24. Greer BE, Berek JS, eds. Current Topics In Obstetrics And Gynecology: Gynecologic Oncology: Treatment Rationale And Techniques. Elsevier; 1991.
25. Forner DM, Lampe B. Exenteration in the treatment of stage III/IV vulvar cancer. Gynecol Oncol 2012;124:87–91.
26. Miller B, Morris M, Levenback C, et al. Pelvic exenteration for primary and recurrent vulvar cancer. Gynecol Oncol 1995;58:202–205.
27. Hoffman MS, Cavanagh D, Roberts WS, et al. Ultraradical surgery for advanced carcinoma of the vulva: an update. Int J Gynecol Cancer 1993;3:369–372.
28. Gadducci A, Cionini L, Romanini A, et al. Old and new perspectives in the management of high-risk, locally advanced or recurrent, and metastatic vulvar cancer. Crit Rev Oncol Hematol 2006;60:227–241.
29. Boronow RC. Combined therapy as an alternative to exenteration for locally advanced vulvo-vaginal cancer: rationale and results. Cancer 1982; 49:1085–1091.
30. Fuh KC, Berek JS. Current management of vulvar cancer. Hematol Oncol Clin North Am 2012;26:45–62.
31. Leiserowitz GS, Russell AH, Kinney WK, et al. Prophylactic chemoradiation of inguinofemoral lymph nodes in patients with locally extensive vulvar cancer. Gynecol Oncol 1997;66:509–514.
32. Russell AH, Mesic JB, Scudder SA, et al. Synchronous radiation and cytotoxic chemotherapy for locally advanced or recurrent squamous cancer of the vulva. Gynecol Oncol 1992;47:14–20.
33. Thomas G, Dembo A, DePetrillo A, et al. Concurrent radiation and chemotherapy in vulvar carcinoma. Gynecol Oncol 1989;34:263–267.
34. Eifel PJ, Morris M, Burke TW, et al. Prolonged continuous infusion cisplatin and 5-fluorouracil with radiation for locally advanced carcinoma of the vulva. Gynecol Oncol 1995;59:51–56.
35. Lupi G, Raspagliesi F, Zucali R, et al. Combined preoperative chemoradiotherapy followed by radical surgery in locally advanced vulvar carcinoma. A pilot study. Cancer 1996;77:1472–1478.
36. Moore DH, Thomas GM, Montana GS, et al. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. Int J Radiat Oncol Biol Phys 1998;42:79–85.
37. Geisler JP, Manahan KJ, Buller RE. Neoadjuvant chemotherapy in vulvar cancer: avoiding primary exenteration. Gynecol Oncol 2006;100:53–57.
38. Landoni F, Maneo A, Zanetta G, et al. Concurrent preoperative chemotherapy with 5-fluorouracil and mitomycin C and radiotherapy (FUMIR) followed by limited surgery in locally advanced and recurrent vulvar carcinoma. Gynecol Oncol 1996;61:321–327.
39. Berek JS, Heaps JM, Fu YS, et al. Concurrent cisplatin and 5-fluorouracil chemotherapy and radiation therapy for advanced-stage squamous carcinoma of the vulva. Gynecol Oncol 1991;42:197–201.
40. Koh WJ, Wallace HJ 3rd, Greer BE, et al. Combined radiotherapy and chemotherapy in the management of local-regionally advanced vulvar cancer. Int J Radiat Oncol Biol Phys 1993;26:809–816.
41. Cunningham MJ, Goyer RP, Gibbons SK, et al. Primary radiation, cisplatin, and 5-fluorouracil for advanced squamous carcinoma of the vulva. Gynecol Oncol 1997;66:258–261.
42. Gerszten K, Selvaraj RN, Kelley J, et al. Preoperative chemoradiation for locally advanced carcinoma of the vulva. Gynecol Oncol 2005;99: 640–644.
43. Tans L, Ansink AC, van Rooij PH, et al. The role of chemo-radiotherapy in the management of locally advanced carcinoma of the vulva: single institutional experience and review of literature. Am J Clin Oncol 2011; 34:22–26.
44. Han SC, Kim DH, Higgins SA, et al. Chemoradiation as primary or adjuvant treatment for locally advanced carcinoma of the vulva. Int J Radiat Oncol Biol Phys 2000;47:1235–1244.
45. Rao YJ, Chin RI, Hui C, et al. Improved survival with definitive chemoradiation compared to definitive radiation alone in squamous cell carcinoma of the vulva: a review of the National Cancer Database. Gynecol Oncol 2017;146:572–579.
46. Montana GS, Thomas GM, Moore DH, et al. Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study. Int J Radiat Oncol Biol Phys 2000;48:1007–1013.
47. Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. Gynecol Oncol 2012;124:529–533.
48. van Triest B, Rasing M, van der Velden J, et al. Phase II study of definitive chemoradiation for locally advanced squamous cell cancer of the vulva: an efficacy study. Gynecol Oncol 2021;163:117–124.
49. Natesan D, Hong JC, Foote J, et al. Primary versus preoperative radiation for locally advanced vulvar cancer. Int J Gynecol Cancer 2017;27: 794–804.
50. Shylasree TS, Bryant A, Howells RE. Chemoradiation for advanced primary vulval cancer. Cochrane Database Syst Rev 2011;2011:CD003752.
51. van Doorn HC, Ansink A, Verhaar-Langereis M, et al. Neoadjuvant chemoradiation for advanced primary vulvar cancer. Cochrane Database Syst Rev 2006;2006:CD003752.
52. Reade CJ, Eiriksson LR, Mackay H. Systemic therapy in squamous cell carcinoma of the vulva: current status and future directions. Gynecol Oncol 2014;132:780–789.
53. Candelaria M, Garcia-Arias A, Cetina L, et al. Radiosensitizers in cervical cancer. Cisplatin and beyond. Radiat Oncol 2006;1:15.
54. Lorvidhaya V, Chitapanarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. Int J Radiat Oncol Biol Phys 2003;55:1226–1232.
55. Cerrotta A, Gardan G, Cavina R, et al. Concurrent radiotherapy and weekly paclitaxel for locally advanced or recurrent squamous cell carcinoma of the uterine cervix. A pilot study with intensification of dose. Eur J Gynaecol Oncol 2002;23:115–119.
56. Pattaranutaporn P, Thirapakawong C, Chansilpa Y, et al. Phase II study of concurrent gemcitabine and radiotherapy in locally advanced stage IIIB cervical carcinoma. Gynecol Oncol 2001;81:404–407.
57. Han SN, Vergote I, Amant F. Weekly paclitaxel/carboplatin in the treatment of locally advanced, recurrent, or metastatic vulvar cancer. Int J Gynecol Cancer 2012;22:865–868.
58. Witteveen PO, van der Velden J, Vergote I, et al. Phase II study on paclitaxel in patients with recurrent, metastatic or locally advanced vulvar cancer not amenable to surgery or radiotherapy: a study of the EORTC-GCG (European Organisation for Research and Treatment of Cancer—Gynaecological Cancer Group). Ann Oncol 2009;20: 1511–1516.
59. 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.
60. Jolly S, Soni P, Gaffney DK, et al. ACR Appropriateness Criteria adjuvant therapy in vulvar cancer. Oncology (Williston Park) 2015;29:867–872; 874–865.
61. Homesley HD, Bundy BN, Sedlis A, et al. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. Obstet Gynecol 1986;68:733–740.
62. Kunos C, Simpkins F, Gibbons H, et al. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. Obstet Gynecol 2009;114:537–546.
63. Swanick CW, Eifel PJ, Huo J, et al. Challenges to delivery and effectiveness of adjuvant radiation therapy in elderly patients with node-positive vulvar cancer. Gynecol Oncol 2017;146:87–93.
64. Fons G, Groenen SM, Oonk MH, et al. Adjuvant radiotherapy in patients with vulvar cancer and one intra capsular lymph node metastasis is not beneficial. Gynecol Oncol 2009;114:343–345.
65. Mahner S, Jueckstock J, Hilpert F, et al. Adjuvant therapy in lymph node-positive vulvar cancer: the AGO-CaRE-1 study. J Natl Cancer Inst 2015;107:dju426.
66. Parthasarathy A, Cheung MK, Osann K, et al. The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. Gynecol Oncol 2006;103:1095–1099.
67. Woelber L, Eulenburg C, Choschzick M, et al. Prognostic role of lymph node metastases in vulvar cancer and implications for adjuvant treatment. Int J Gynecol Cancer 2012;22:503–508.
68. Gill BS, Bernard ME, Lin JF, et al. Impact of adjuvant chemotherapy with radiation for node-positive vulvar cancer: a National Cancer Data Base (NCDB) analysis. Gynecol Oncol 2015;137:365–372.
69. Swanick CW, Smith GL, Huo J, et al. Delivery and outcomes of adjuvant radiation therapy in older women with node-positive vulvar cancer. Oncology (Williston Park) 2016;30(Suppl 1):Abstract P021.
70. Ignatov T, Eggemann H, Burger E, et al. Adjuvant radiotherapy for vulvar cancer with close or positive surgical margins. J Cancer Res Clin Oncol 2016;142:489–495.
71. Viswanathan AN, Pinto AP, Schultz D, et al. Relationship of margin status and radiation dose to recurrence in post-operative vulvar carcinoma. Gynecol Oncol 2013;130:545–549.

72. Van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J Clin Oncol 2008; 26:884–889.
73. van Beekhuizen HJ, Auzin M, van den Einden LC, et al. Lymph node count at inguinofemoral lymphadenectomy and groin recurrences in vulvar cancer. Int J Gynecol Cancer 2014;24:773–778.
74. Bell JG, Lea JS, Reid GC. Complete groin lymphadenectomy with preservation of the fascia lata in the treatment of vulvar carcinoma. Gynecol Oncol 2000;77:314–318.
75. Stehman FB, Bundy BN, Dvoretsky PM, et al. Early stage I carcinoma of the vulva treated with ipsilateral superficial inguinal lymphadenectomy and modified radical hemivulvectomy: a prospective study of the Gynecologic Oncology Group. Obstet Gynecol 1992;79:490–497.
76. Kirby TO, Rocconi RP, Numnum TM, et al. Outcomes of stage I/II vulvar cancer patients after negative superficial inguinal lymphadenectomy. Gynecol Oncol 2005;98:309–312.
77. Gonzalez Bosquet J, Magrina JF, Gaffey TA, et al. Long-term survival and disease recurrence in patients with primary squamous cell carcinoma of the vulva. Gynecol Oncol 2005;97:828–833.
78. Nooij LS, van den Brand FA, Gaarenstroom KN, et al. Risk factors and treatment for recurrent vulvar squamous cell carcinoma. Crit Rev Oncol Hematol 2016;106:1–13.
79. Gien LT, Sutradhar R, Thomas G, et al. Patient, tumor, and health system factors affecting groin node dissection rates in vulvar carcinoma: a population-based cohort study. Gynecol Oncol 2015;139:465–470.
80. 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.
81. Maggino T, Landoni F, Sartori E, et al. Patterns of recurrence in patients with squamous cell carcinoma of the vulva. A multicenter CTF Study. Cancer 2000;89:116–122.
82. Mahner S, Prieske K, Grimm D, et al. Systemic treatment of vulvar cancer. Expert Rev Anticancer Ther 2015;15:629–637.
83. Salom EM, Penalver M. Recurrent vulvar cancer. Curr Treat Options Oncol 2002;3:143–153.
84. Piura B, Masotina A, Murdoch J, et al. Recurrent squamous cell carcinoma of the vulva: a study of 73 cases. Gynecol Oncol 1993;48: 189–195.
85. Raffetto N, Tombolini V, Santarelli M, et al. Radiotherapy alone and chemoirradiation in recurrent squamous cell carcinoma of the vulva. Anticancer Res 2003;23:3105–3108.
86. Podratz KC, Symmonds RE, Taylor WF, et al. Carcinoma of the vulva: analysis of treatment and survival. Obstet Gynecol 1983;61:63–74.
87. Chiantera V, Rossi M, De Iaco P, et al. Morbidity after pelvic exenteration for gynecological malignancies: a retrospective multicentric study of 230 patients. Int J Gynecol Cancer 2014;24:156–164.
88. Stehman FB, Bundy BN, Ball H, et al. Sites of failure and times to failure in carcinoma of the vulva treated conservatively: a Gynecologic Oncology Group study. Am J Obstet Gynecol 1996;174:1128–1132; discussion 1132–1133.
89. Hopkins MP, Reid GC, Morley GW. The surgical management of recurrent squamous cell carcinoma of the vulva. Obstet Gynecol 1990;75: 1001–1005.
90. Bellati F, Angioli R, Manci N, et al. Single agent cisplatin chemotherapy in surgically resected vulvar cancer patients with multiple inguinal lymph node metastases. Gynecol Oncol 2005;96:227–231.
91. Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet 2017;390:1654–1663.
92. Rosen VM, Guerra I, McCormack M, et al. Systematic review and network meta-analysis of bevacizumab plus first-line topotecan-paclitaxel or cisplatin-paclitaxel versus non-bevacizumab-containing therapies in persistent, recurrent, or metastatic cervical cancer. Int J Gynecol Cancer 2017;27:1237–1246.
93. Kitagawa R, Katsumata N, Shibata T, et al. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505. J Clin Oncol 2015;33:2129–2135.
94. Lorusso D, Petrelli F, Coinu A, et al. A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer. Gynecol Oncol 2014;133:117–123.
95. Santeufemia DA, Capobianco G, Re GL, et al. Cisplatin-gemcitabine as palliative chemotherapy in advanced squamous vulvar carcinoma: report of two cases. Eur J Gynaecol Oncol 2012;33:421–422.
96. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2009;27:4649–4655.
97. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med 2018;379:341–351.
98. Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med 2022;386:544–555.
99. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol 2016;39:98–106.
100. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy–inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–6587.
101. Wherry EJ. T cell exhaustion. Nat Immunol 2011;12:492–499.
102. Hecking T, Thiesler T, Schiller C, et al. Tumoral PD-L1 expression defines a subgroup of poor-prognosis vulvar carcinomas with non-viral etiology. Oncotarget 2017;8:92890–92903.
103. Howitt BE, Sun HH, Roemer MG, et al. Genetic basis for PD-L1 expression in squamous cell carcinomas of the cervix and vulva. JAMA Oncol 2016;2:518–522.
104. Naing A, Meric-Bernstam F, Stephen B, et al. Phase 2 study of pembrolizumab in patients with advanced rare cancers. J Immunother Cancer 2020;8:e000347.
105. How JA, Jazaeri AA, Soliman PT, et al. Pembrolizumab in vaginal and vulvar squamous cell carcinoma: a case series from a phase II basket trial. Sci Rep 2021;11:3667.
106. Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2019;37:1470–1478.
107. Shapira-Frommer R, Mileshkin L, Manzyuk L, et al. Efficacy and safety of pembrolizumab for patients with previously treated advanced vulvar squamous cell carcinoma: results from the phase 2 KEYNOTE-158 study. Gynecol Oncol 2022;166:211–218.
108. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353–1365.
109. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/ repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1–10.
110. US FDA. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. Accessed November 8, 2023. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication
111. US FDA. FDA approves pembrolizumab for adults and children with TMB-H solid tumors. Accessed November 8, 2023. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors
112. Naumann RW, Hollebecque A, Meyer T, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 358 trial. J Clin Oncol 2019;37:2825–2834.
113. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271–282.
114. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731–739.
115. Hong DS, Bauer TM, Lee JJ, et al. Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study. Ann Oncol 2019;30:325–331.
116. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020;21:531–540.
117. Dessources K, Aviki E, Leitao MM Jr. Lower extremity lymphedema in patients with gynecologic malignancies. Int J Gynecol Cancer 2020;30:252–260.

118. Bona AF, Ferreira KR, Carvalho RBM, et al. Incidence, prevalence, and factors associated with lymphedema after treatment for cervical cancer: a systematic review. Int J Gynecol Cancer 2020;30:1697–1704.
119. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline update. J Clin Oncol 2020;38:3325–3348.
120. Stahl JM, Qian JM, Tien CJ, et al. Extended duration of dilator use beyond 1 year may reduce vaginal stenosis after intravaginal high-dose-rate brachytherapy. Support Care Cancer 2019;27:1425–1433.
121. Park HS, Ratner ES, Lucarelli L, et al. Predictors of vaginal stenosis after intravaginal high-dose-rate brachytherapy for endometrial carcinoma. Brachytherapy 2015;14:464–470.
122. Dracham CB, Shankar A, Madan R. Radiation induced secondary malignancies: a review article. Radiat Oncol J 2018;36:85–94.
123. Borella F, Preti M, Bertero L, et al. Is there a place for immune checkpoint inhibitors in vulvar neoplasms? A state of the art review. Int J Mol Sci 2020;22:190.
124. Schepisi G, Casadei C, Toma I, et al. Immunotherapy and its development for gynecological (ovarian, endometrial and cervical) tumors: from immune checkpoint inhibitors to chimeric antigen receptor (CAR)-T cell therapy. Cancers (Basel) 2021;13:840.
125. Lin KY, Frawley HC, Denehy L, et al. Exercise interventions for patients with gynaecological cancer: a systematic review and meta-analysis. Physiotherapy 2016;102:309–319.
126. Nekhlyudov L, Mollica MA, Jacobsen PB, et al. Developing a quality of cancer survivorship care framework: implications for clinical care, research, and policy. J Natl Cancer Inst 2019;111:1120–1130.
127. Bober SL, Reese JB, Barbera L, et al. How to ask and what to do: a guide for clinical inquiry and intervention regarding female sexual health after cancer. Curr Opin Support Palliat Care 2016;10:44–54. https://journals.lww.com/co-supportiveandpalliativecare/Fulltext/2016/03000/How_to_ask_and_what_to_do__a_guide_for_clinical.12.aspx
128. Damast S, Jeffery DD, Son CH, et al. Literature review of vaginal stenosis and dilator use in radiation oncology. Pract Radiat Oncol 2019;9:479–491.
129. Campbell G, Thomas TH, Hand L, et al. Caring for survivors of gynecologic cancer: assessment and management of long-term and late effects. Semin Oncol Nurs 2019;35:192–201.
130. Society of Gynecologic Oncology. Survivorship toolkit. Accessed November 8, 2023. Available at: https://www.sgo.org/resources/survivorship-toolkit/

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The NCCN Guidelines Staff have no conflicts to disclose.

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