National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Vulvar Cancer (Squamous Cell Carcinoma)

Version 1.2016

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Vulvar Cancer (Squamous Cell Carcinoma)

NCCN Guidelines Index
Vulvar Cancer TOC
Discussion

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NCCN Guidelines Index
Vulvar Cancer TOC
Discussion

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016 Table of Contents
Vulvar Cancer (Squamous Cell Carcinoma)

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

NCCN Guidelines Version 1.2016
Vulvar Cancer (Squamous Cell Carcinoma)

SQUAMOUS CELL CARCINOMA[a]

WORKUP

- **H&P**
- **CBC**
- **Biopsy, pathologic review**
- **LFT/renal function studies**
- **Imaging**[b] **(CT/PET/MRI) as needed for delineating extent of tumor or for treatment planning**
- **EUA cystoscopy or proctoscopy as indicated**
- **Smoking cessation and counseling intervention if indicated (See NCCN Guidelines for Smoking Cessation)**

CLINICAL STAGE	PRIMARY TREATMENT
Early Stage: • **T1, Smaller T2**[c]	See Primary Treatment (VULVA-2)
Locally advanced: • **Larger T2, T3 (non-visceral–sparing primary surgery)**	See Primary Treatment (VULVA-5)
Metastatic disease beyond pelvis: • **Any T, Any N, M1 beyond pelvis**	See Primary Treatment (VULVA-7)

[a]Histologic high-grade squamous intraepithelial lesion (HSIL; formerly defined as carcinoma in situ [CIS] and incorporates vulvar intraepithelial neoplasia 2 and 3 [VIN2/3]) can be treated with wide local excision.
[b]CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT.
[c]Smaller T2 tumors: ≤4 cm, without involvement of the urethra, vagina, or anus.

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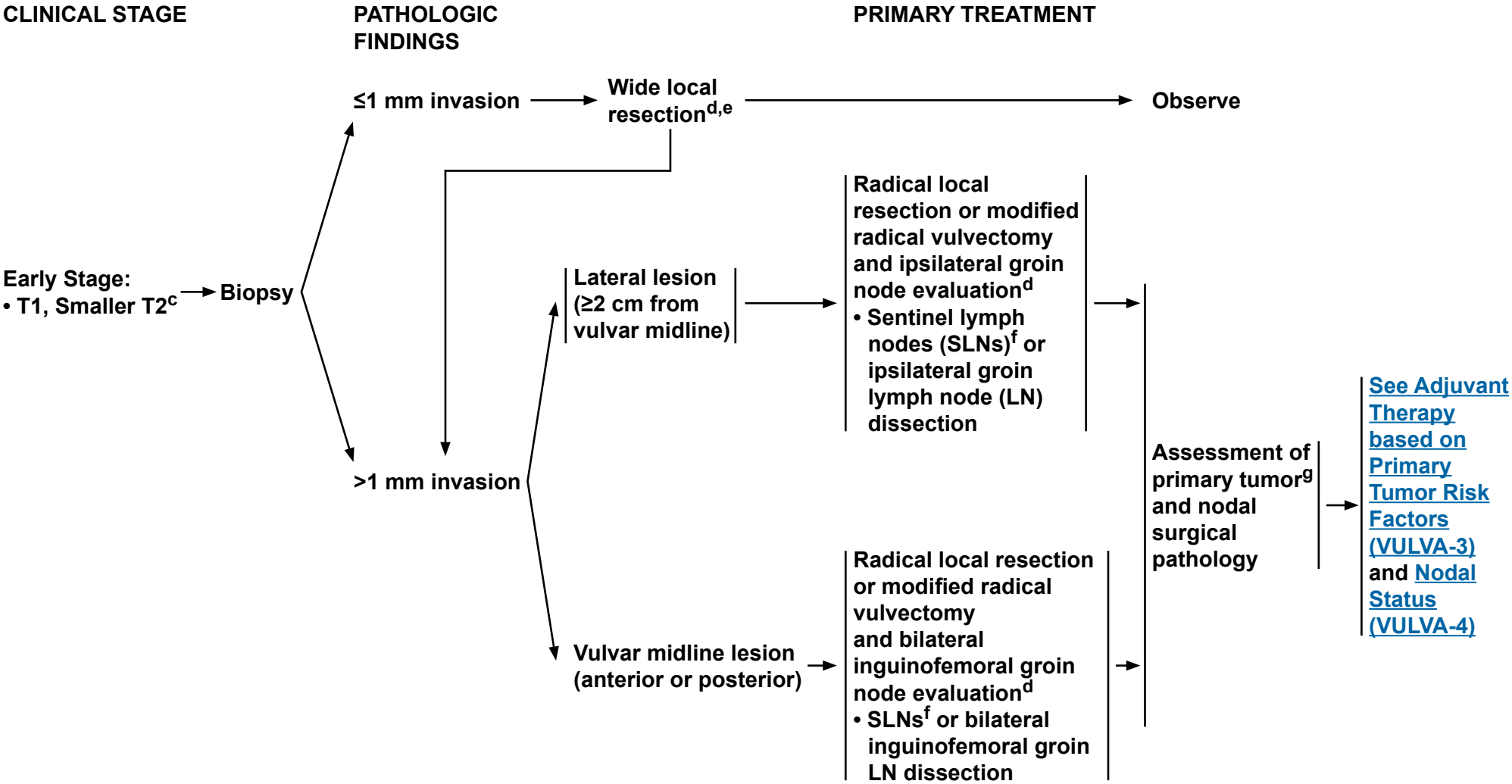
NCCN Guidelines Version 1.2016
Vulvar Cancer (Squamous Cell Carcinoma)

NCCN Guidelines Index
Vulvar Cancer TOC
Discussion



[c]Smaller T2 tumors: ≤4 cm, without involvement of the urethra, vagina, or anus.
[d]See Principles of Surgery (VULVA-A).
[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 Vulvar Surgery: Tumor Margin Status (VULVA-A 1 of 4).

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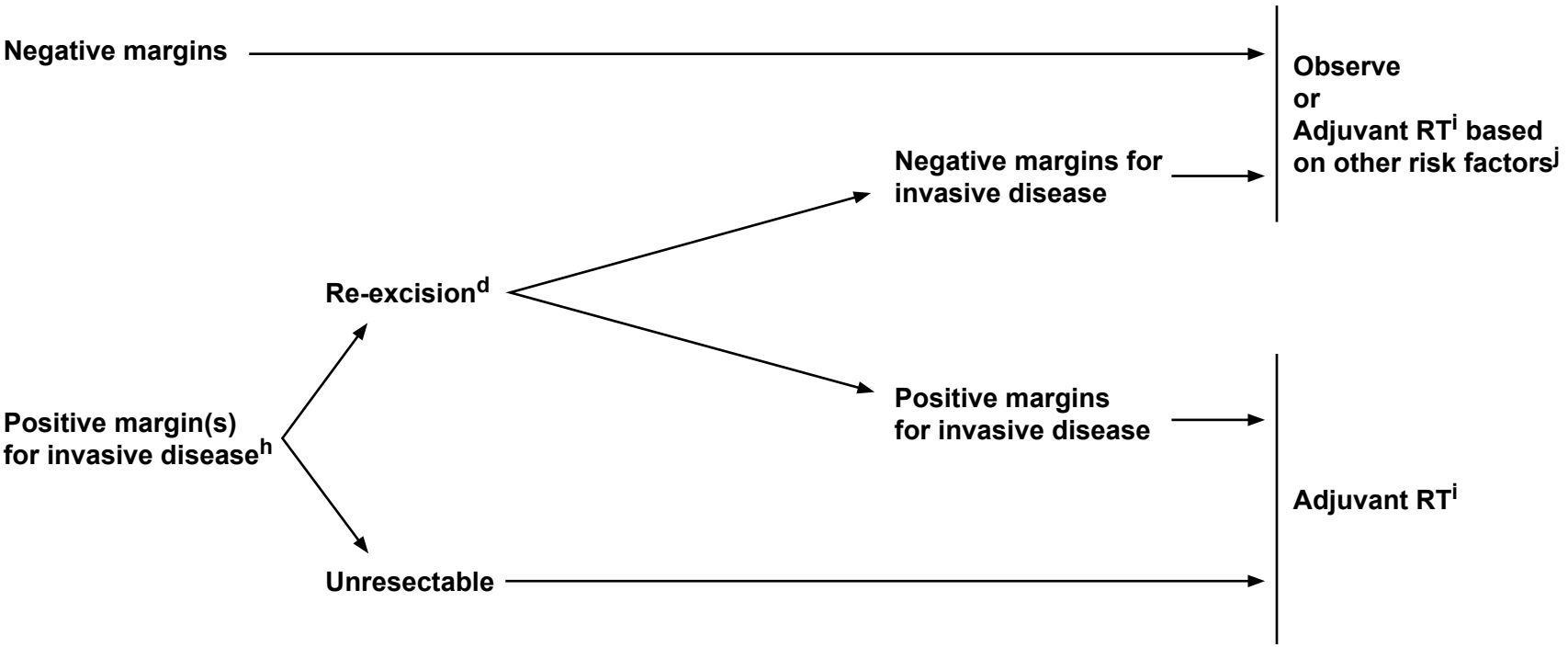
PRIMARY TUMOR RISK FACTORS

ADJUVANT THERAPY TO THE PRIMARY SITE



[d] See Principles of Surgery (VULVA-A).
[h] The management of positive margins for HSIL (non-invasive disease) should be individualized.
[i] See Principles of Radiation Therapy (VULVA-B).
[j] Other primary risk factors include: lymphovascular invasion, negative but close tumor margins (<8 mm), tumor size, depth of invasion, pattern of invasion (spray or diffuse). Nodal involvement (as an indicator of lymphovascular space invasion) may also impact selection of adjuvant therapy to the primary site.

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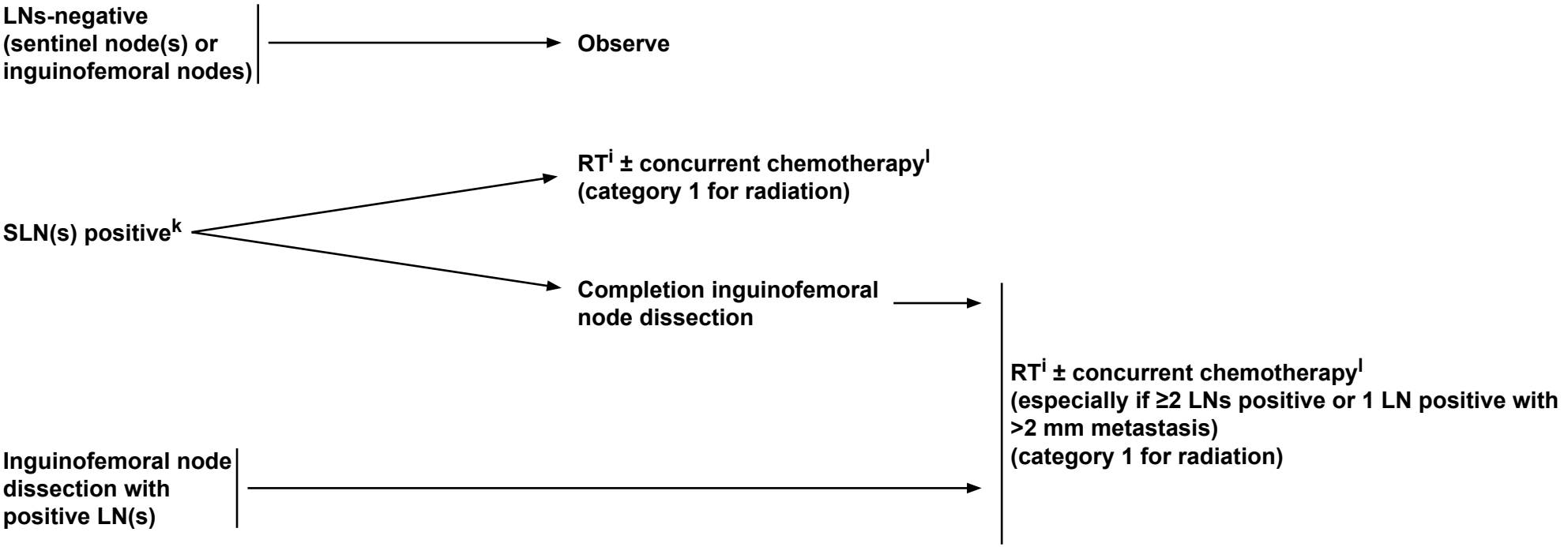
See Surveillance (VULVA-8)

ADJUVANT THERAPY TO THE NODES

NODAL EVALUATION



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

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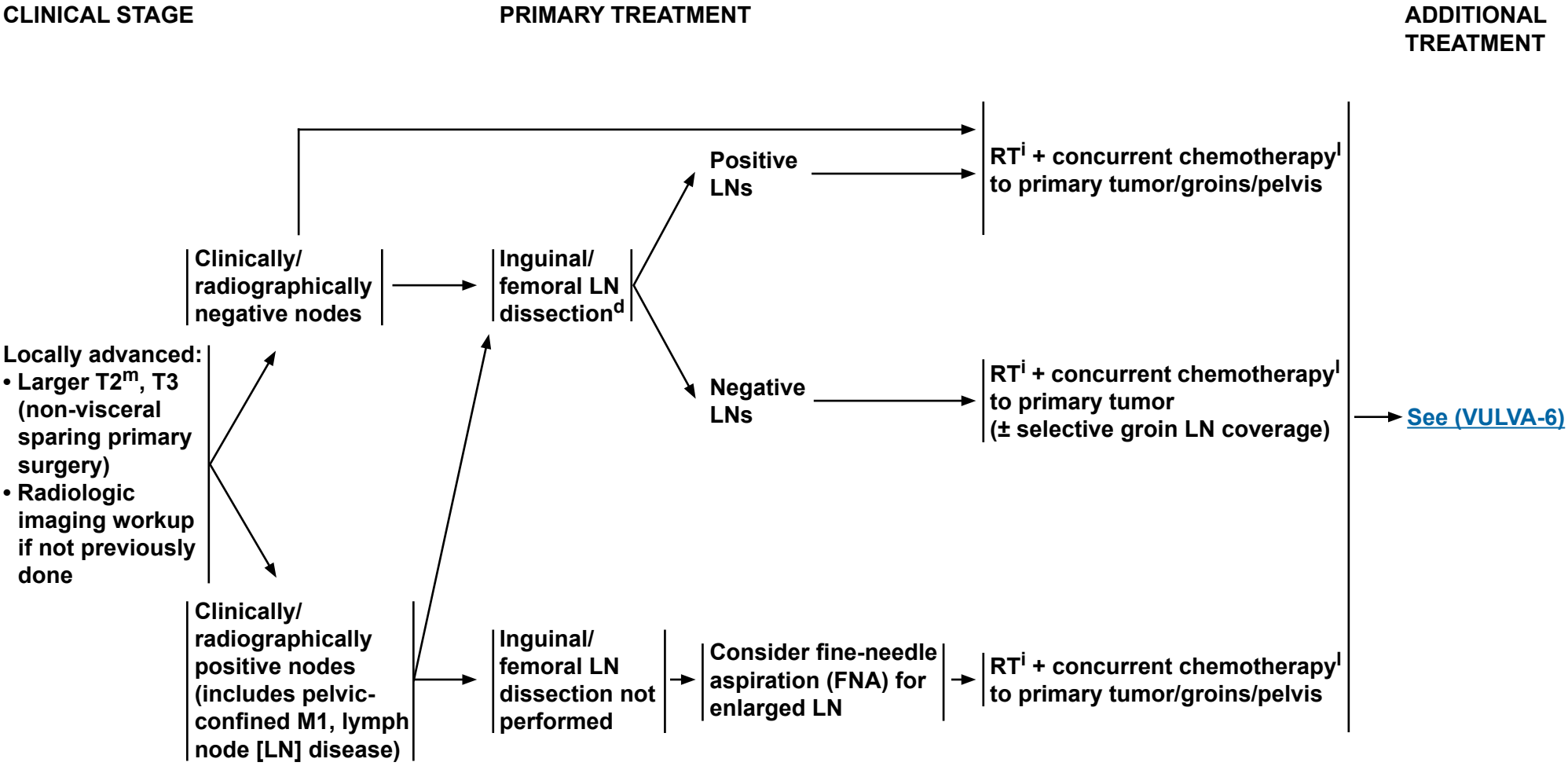
See Surveillance (VULVA-8)

NCCN Guidelines Version 1.2016
Vulvar Cancer (Squamous Cell Carcinoma)



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

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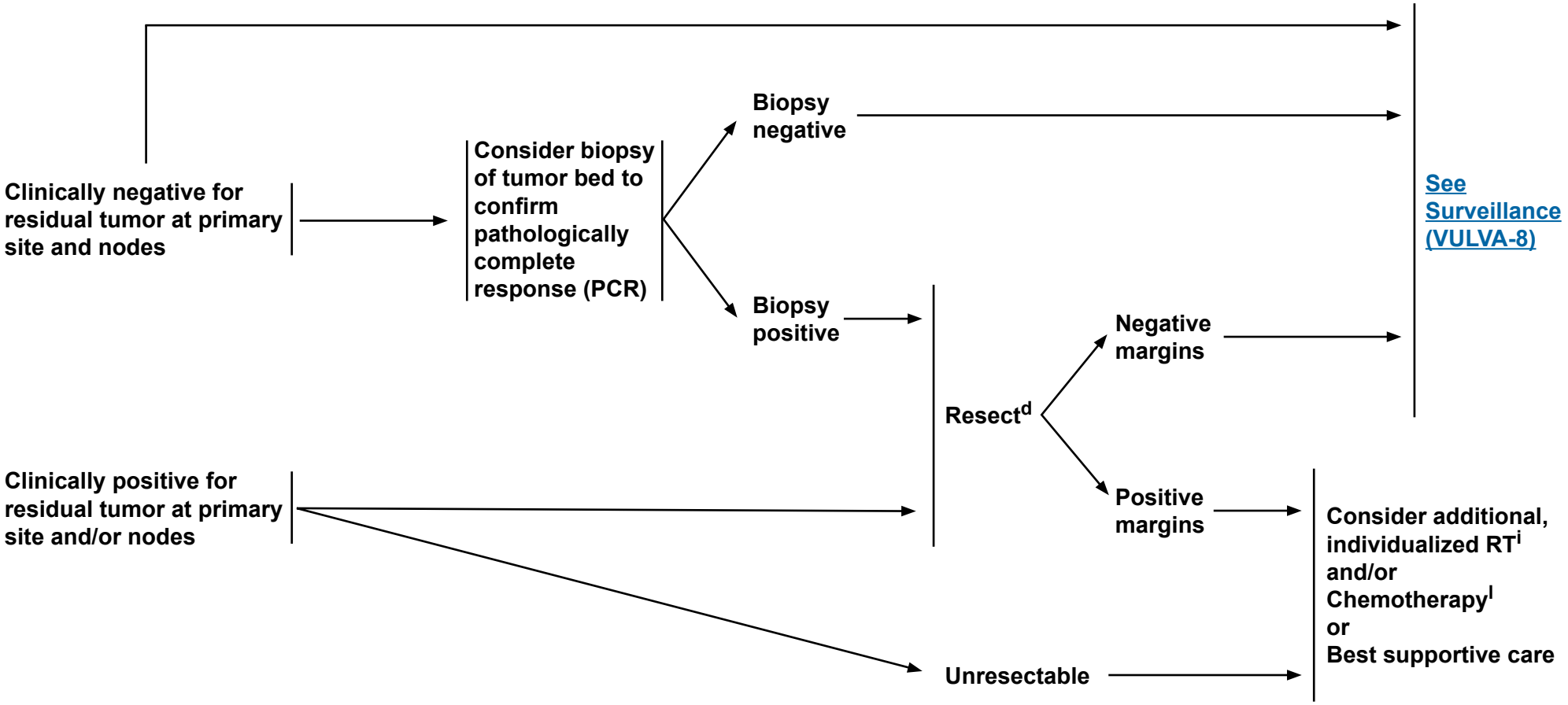
EVALUATION OF RESPONSE **ADDITIONAL TREATMENT**



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

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CLINICAL STAGE	PRIMARY TREATMENT
Metastatic disease beyond pelvis: • **Any T, Any N, M1 beyond pelvis**	**RT[i] for locoregional control/symptom palliation** **and/or** **Chemotherapy[l]** **or** **Best supportive care (See NCCN Guidelines for Palliative Care)**

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

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SURVEILLANCE[n]

- **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[o] as indicated for the detection of lower genital tract neoplasia**
- **Imaging (chest radiography, CT, PET, PET/CT, MRI) as indicated based on symptoms or examination findings suspicious for recurrence**
- **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, smoking cessation, and nutrition counseling (See NCCN Guidelines for Survivorship and NCCN Guidelines for Smoking Cessation)**
- **Patient education regarding sexual health, vaginal dilator use, and vaginal lubricants/moisturizers (eg, estrogen creams)**

WORKUP

Clinically suspect recurrence

- **Metastatic workup with imaging**
- **Consider biopsy to confirm distant metastasis**

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

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

[n]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.

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

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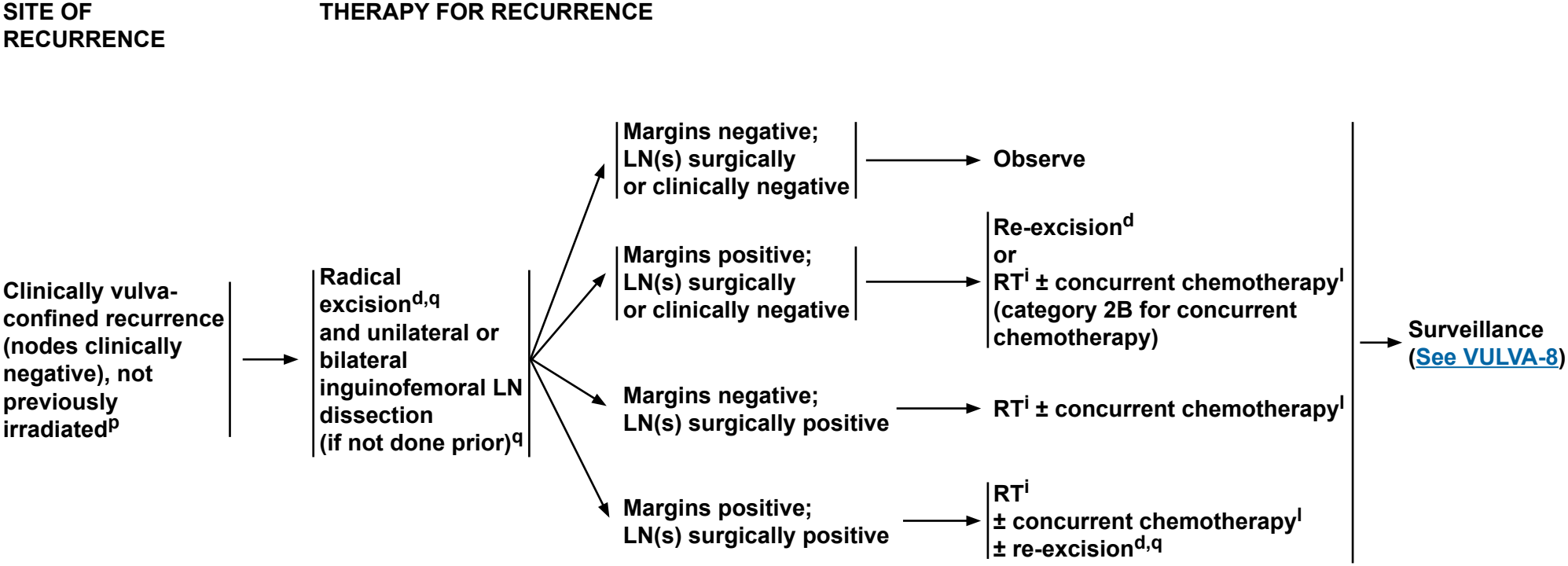

[d] See Principles of Surgery (VULVA-A).
[i] See Principles of Radiation Therapy (VULVA-B).
[l] See Systemic Therapy (VULVA-C).
[p] For patients who previously received chemoradiation, see Additional Treatment (VULVA-6).
[q] Consider pelvic exenteration for large central recurrence.

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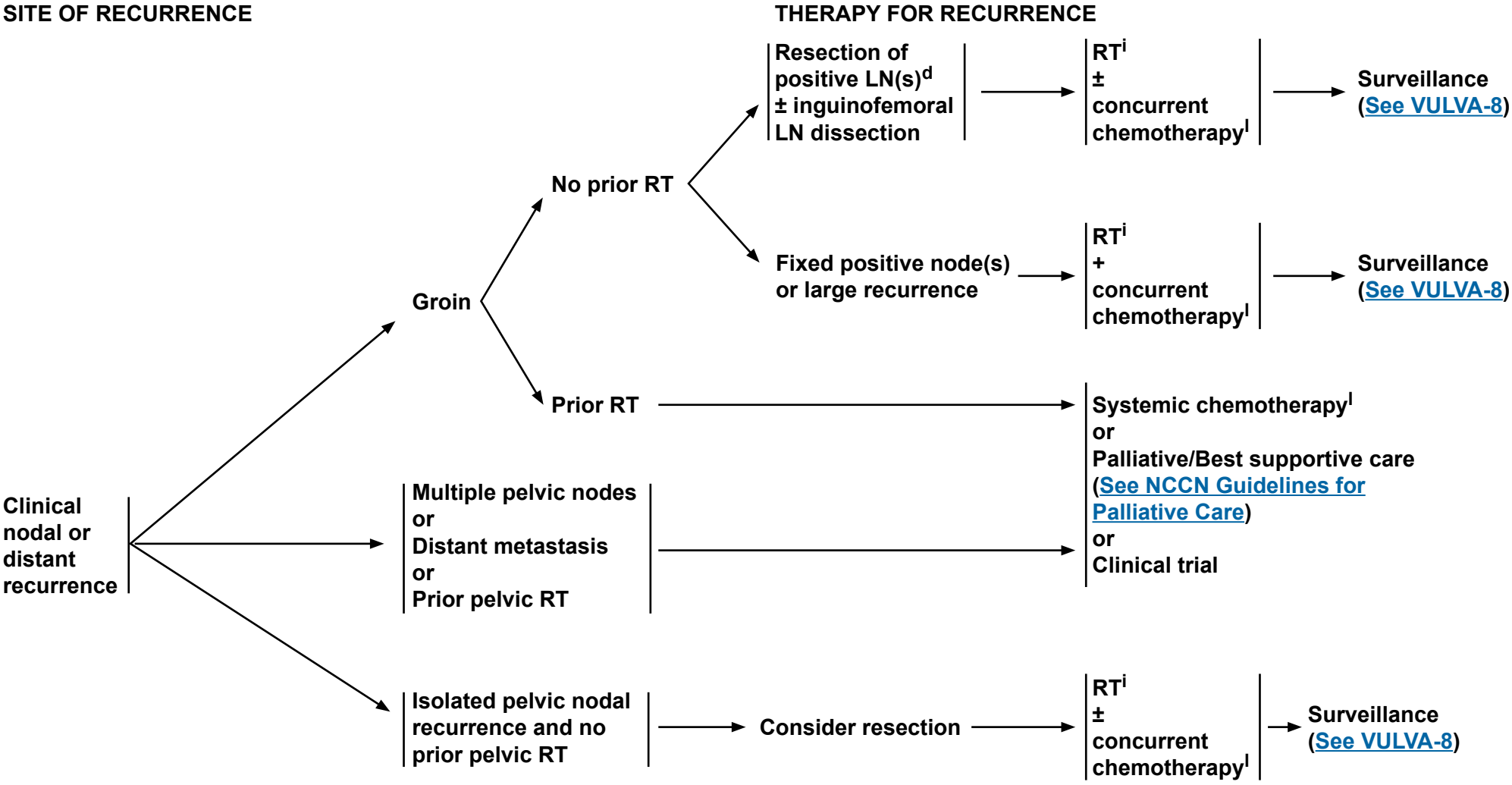
NCCN Guidelines Version 1.2016
Vulvar Cancer (Squamous Cell Carcinoma)

NCCN Guidelines Index
Vulvar Cancer TOC
Discussion



[d] See Principles of Surgery (VULVA-A).
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PRINCIPLES OF VULVAR 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 RT ± 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]**

[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]

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PRINCIPLES OF VULVAR SURGERY: SURGICAL STAGING

- Vulvar cancer is staged using the American Joint Commission 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 a 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 <2 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-A 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]

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PRINCIPLES OF VULVAR SURGERY: INGUINOFEMORAL SENTINEL LYMPH NODE PROCEDURE

- 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 RT.

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PRINCIPLES OF VULVAR SURGERY: REFERENCES

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PRINCIPLES OF RADIATION

General Principles

- 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.

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.

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

PRINCIPLES OF RADIATION

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.
- 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.
- 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 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 radiation in select cases such as vulva edema or marked tumor regression.
- Planning should be taken with care to respect normal tissue tolerances such as rectum, bladder, small bowel, and femoral head and neck.[4]

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

PRINCIPLES OF RADIATION
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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**
- **Cisplatin/vinorelbine**
- **Cisplatin/paclitaxel**

[1]Reade CJ, Eiriksson LR, Mackay H. Systemic chemotherapy in squamous cell carcinoma of the vulva: Current status and future directions. Gynecol Oncol 2014;132:780-789.
[2]Anal cancer literature supports the use of mitomycin-based regimens based on high quality evidence. Chin JY, Hong TS, Ryan DP. Mitomycin in anal cancer: still the standard of care. J Clin Oncol 2012;30:4297.

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

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

Primary Tumor (T)

TNM Categories	FIGO Stages	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1a	**A**	Lesions 2 cm or less in size, confined to the vulva or perineum and with stromal invasion 1.0 mm or less**
T1b	**IB**	Lesions more than 2 cm in size or any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum
T2***	**II**	Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)
T3******	**IVA**	Tumor of any size with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

*Note: FIGO no longer includes Stage 0 (Tis).
**Note: The depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
***FIGO uses the classification T2/T3. This is defined as T2 in TNM.
****FIGO uses the classification T4. This is defined as T3 in TNM.

Regional Lymph Nodes (N)

TNM Categories	FIGO Stages	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		One or two regional lymph nodes with the following features
N1a	**IIIA**	1 or 2 lymph node metastases each 5 mm or less
N1b	**IIIA**	One lymph node metastasis 5 mm or greater
N2	**IIIB**	Regional lymph node metastasis with the following features
N2a	**IIIB**	Three or more lymph node metastases each less than 5 mm
N2b	**IIIB**	Two or more lymph node metastases 5 mm or greater
N2c	**IIIC**	Lymph node metastasis with extra-capsular spread
N3	**IVA**	Fixed or ulcerated regional lymph node metastasis

Distant Metastasis (M)

TNM Categories	FIGO Stages	
M0		No distant metastasis
M1	**IVB**	Distant metastasis (including pelvic lymph node metastasis)

For the original FIGO staging tables see: Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2009;105:103-104. Copyright 2009.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.