National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Vaginal Cancer

NCCN Evidence Blocks™

Version 5.2025 — April 7, 2025

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

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

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

NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

NCCN Categories of Preference

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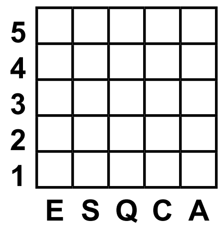
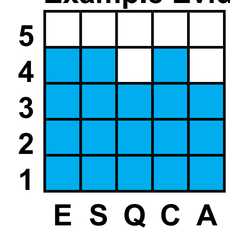
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

WORKUP[a]

- **History and physical (H&P) (include sexual history, immunosuppression, prior hysterectomy, smoking history, gynecologic and anorectal symptoms)**
- **Pelvic exam (bimanual and rectovaginal), cervical evaluation and pap smear, colposcopy, vulvar evaluation**
- **Rule out synchronous anorectal, cervical, endometrial, or vulvar primary with vaginal metastasis or extension, or recurrent disease from prior malignancy[b]**
- **Consider examination under anesthesia (EUA) with biopsies (consider cystoscopy/ proctoscopy) as clinically indicated[c]**
- **Imaging[d]**
- **Complete blood count (CBC), comprehensive metabolic panel (CMP)**
- **Human papillomavirus (HPV) and human immunodeficiency virus (HIV) testing in select patients**

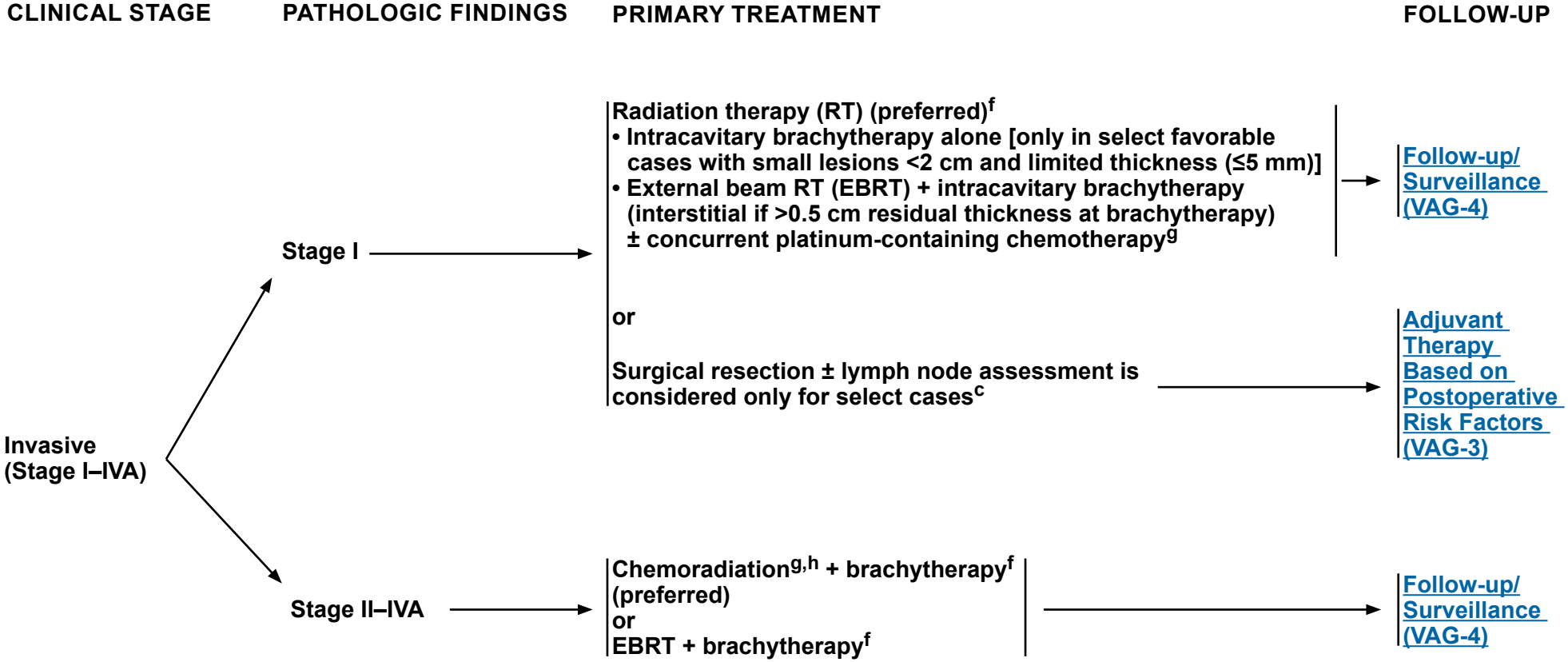
CLINICAL STAGE[e]

Invasive (Stage I–IVA) → **VAG-2**

Distant metastatic (Stage IVB) → **VAG-6**

[a] Multidisciplinary expertise is recommended. Consider referral to a center of expertise that specializes in the treatment of vaginal cancers.
[b] Only a minority of vaginal cancers originate in the vagina. The remaining are generally metastatic from other sites. If vaginal lesion(s) involve the cervix or vulva, it is not considered vaginal cancer and the appropriate treatment algorithm should be consulted (see NCCN Guidelines for Cervical Cancer or NCCN Guidelines for Vulvar Cancer).
[c] Principles of Surgery (VAG-E).
[d] Principles of Imaging (VAG-B).
[e] Principles of Pathology (VAG-A).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.



[c] Principles of Surgery (VAG-E).
[f] Principles of Radiation Therapy (VAG-C).
[g] Chemoradiation may not be suitable for all patients. It should be used with caution in patients who are older, frail, and/or have multiple comorbidities.
[h] Concurrent chemotherapy has been shown in many series to improve outcomes and is often used in stage II–IV disease. Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant). See Principles of Systemic Therapy (VAG-D).

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POSTOPERATIVE RISK FACTORS → **ADJUVANT THERAPY TO THE PRIMARY SITE**

- **Negative margins** → **Observe** → [Follow-up/Surveillance (VAG-4)]
- **Close or positive margin(s) for invasive disease or positive lymph nodes**[i] → **Adjuvant RT**[f] **or chemoradiation**[g,j] **and/or Brachytherapy**[f,k] → [Follow-up/Surveillance (VAG-4)]

[f] Principles of Radiation Therapy (VAG-C).
[g] Chemoradiation may not be suitable for all patients. It should be used with caution in patients who are older, frail, and/or have multiple comorbidities.
[i] The management of positive margins for high-grade squamous intraepithelial lesion (HSIL) should be individualized.
[j] See Principles of Systemic Therapy (VAG-D).
[k] In select patients, re-excision may be considered. See Principles of Surgery (VAG-E).

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FOLLOW-UP/ SURVEILLANCE

- **Interval H&P**
  - **every 3–6 mo for 2 y,**
  - **every 6–12 mo for 3–5 y,**
    then annually based on patient's risk of disease recurrence
- **Consider cervical/vaginal cytology screening[l,m] as indicated for the detection of lower genital tract neoplasia (may include HPV testing)**
- **Post-treatment imaging 3–4 mo to assess response**
- **Further imaging as indicated based on symptoms or examination findings suspicious for recurrence[d,n]**
- **Laboratory assessment (CBC, blood urea nitrogen [BUN], creatinine) as indicated based on symptoms or examination findings suspicious for recurrence**
- **Clinical evaluation and management of potential long-term and late effects of treatment and patient education[o] (Also see Principles of Gynecologic Survivorship (VAG-F), NCCN Guidelines for Survivorship, and NCCN Guidelines for Smoking Cessation)**

WORKUP

Clinically suspected recurrence → **• Imaging workup[d] • Biopsy to confirm local and/or distant recurrence** →

- **Therapy for Relapse (Locoregional Recurrence) (VAG-5)**
- **Treatment for Stage IVB or Recurrent Distant Metastases (VAG-6)**

[d] Principles of Imaging (VAG-B).
[l] Regular cytology can be considered for detection of lower genital tract dysplasia, although its value in detection of recurrent genital tract cancer is limited.
[m] The accuracy of cytology results may be affected in patients who have received pelvic radiation.
[n] Recurrences should be proven by biopsy before proceeding to treatment planning.
[o] Patient education should include symptoms of potential recurrence, lifestyle, obesity, exercise, sexual health (including vaginal dilator use and lubricants/moisturizers, local estrogen and hormone therapy for menopause), smoking cessation, and nutrition counseling.

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THERAPY FOR RELAPSE

Locoregional recurrence

- **No prior RT or recurrence outside of previously radiated field** → **EBRT ± brachytherapy[f] or Chemoradiation[f,j,p] ± brachytherapy[f]** → Recurrence
- **Prior intracavitary brachytherapy only** → **Individualized EBRT ± systemic therapy[j,q] ± interstitial brachytherapy[f] ± surgery for select patients[c]** → Recurrence
- **Prior EBRT ± brachytherapy**
  - **Central disease** →
    - **Pelvic exenteration[c] ± intraoperative RT (IORT)[f] (category 3 for IORT)** → Recurrence
    - **or**
    - **Consider reirradiation[f] or local excision[c] in carefully selected patients** → Recurrence
  - **Noncentral disease** → **Systemic therapy[j,q] or Resection[c] ± IORT[f] (category 3 for IORT) or Reirradiation[f] or Best supportive care (NCCN Guidelines for Palliative Care)** → Recurrence

Recurrence → **Systemic therapy[j,q] or Best supportive care (NCCN Guidelines for Palliative Care)**

[c] Principles of Surgery (VAG-E).
[f] Principles of Radiation Therapy (VAG-C).
[j] Systemic Therapy for Vaginal Cancer (VAG-D).
[p] Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant).
[q] Consider additional testing. See Principles of Pathology (VAG-A 2 of 2).

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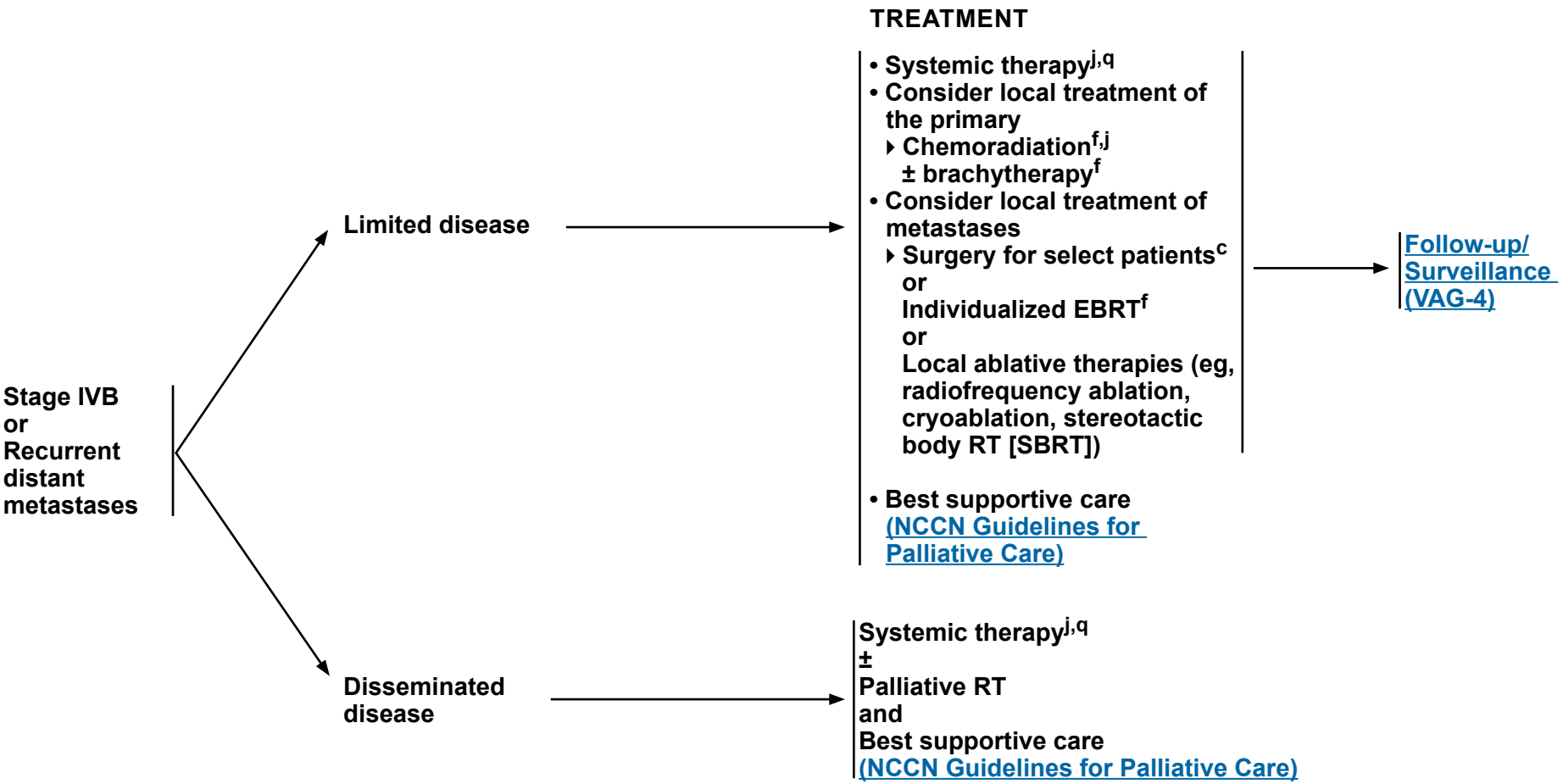

[c] Principles of Surgery (VAG-E).
[f] Principles of Radiation Therapy (VAG-C).
[j] Systemic Therapy for Vaginal Cancer (VAG-D).
[q] Consider additional testing. See Principles of Pathology (VAG-A 2 of 2).

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PRINCIPLES OF PATHOLOGY

General Principles

- **Vaginal carcinomas account for <1% of cancers affecting individuals assigned female at birth (AFAB) worldwide.**
- **The predominant pathway for vaginal squamous intraepithelial lesion (SIL) and vaginal squamous cell carcinoma is HPV infection, predominantly high-risk HPV types with the most common type being HPV16.**
- **For HPV-associated precursors, low-grade SIL (LSIL) or high-grade SIL (HSIL) is preferred; vaginal intraepithelial lesion (VAIN) may also be used and is graded 1, 2, or 3.**
- **The risk of progression from HSIL or VAIN to invasive squamous cell carcinoma approximates 5%. Categorization of vaginal squamous cell carcinoma has been simplified into HPV-associated and HPV-independent types based upon pathogenesis. If association is unknown, inclusion of "not otherwise specified (NOS)" is recommended. Previously used terms, "warty," "basaloid," "verrucous," and "papillary," are no longer necessary components of the histologic type.**
- **HPV-independent squamous cell carcinomas of the vagina are much less common and are often seen in postmenopausal AFAB individuals (median age 73 years). These tumors are predominantly of the keratinizing type histology and demonstrate negative p16 and positive p53 immunohistochemistry (IHC). As with HPV-associated vaginal carcinomas, prior history (<5 years) of cervical and vulvar carcinomas must be excluded.**
- **Other types of vaginal carcinomas are very rare and include: HPV-associated vaginal adenocarcinoma, endometrioid carcinoma, and clear cell carcinoma, mucinous carcinoma (gastric and intestinal types), mesonephric adenocarcinoma, carcinosarcoma, mixed tumor of the vagina, adenocarcinoma of skene gland origin, adenosquamous carcinoma, adenoid basal carcinoma, neuroendocrine carcinomas, adenosarcoma, and germ cell tumors.**

Continued

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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PRINCIPLES OF PATHOLOGY

Pathologic Assessment for Vaginal Carcinoma

- **Procedure type (ie, biopsy, local excision, partial vaginectomy, radical vaginectomy, trachelectomy)**
- **Tumor site (upper, middle, or lower third)**
- **Tumor size: include greatest dimension and additional two dimensions**
- **Histologic types: HPV-associated squamous cell carcinoma, HPV-independent squamous cell carcinoma, HPV-associated vaginal adenocarcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma (gastric and intestinal types), mesonephric adenocarcinoma, carcinosarcoma, mixed tumor of the vagina, adenocarcinoma of skene gland origin, adenosquamous carcinoma, adenoid basal carcinoma, adenosarcoma, neuroendocrine carcinomas, and germ cell tumors**
- **HPV-associated vaginal SILs are divided into the LSIL and HSIL categories; LSIL is associated with both low- and high-risk HPV types and HSIL is exclusively associated with high-risk HPV types**
- **Histologic grade: well, moderately, and poorly differentiated**
- **Lymphovascular space invasion (LVSI)**
- **Precursor lesion(s): VAIN/SIL**
- **Surgical resection margin status**
- **Determination of primary site: Prior (<5 year) history of cervical or vulvar carcinoma must be excluded.**
- **Ancillary testing**
  - **Recommend ancillary testing to determine HPV status either by p16 IHC or RNA in situ hybridization (ISH) or DNA sequencing[a]**
  - **Recommend p53 IHC to determine p53 status in HPV-negative tumors (next-generation sequencing [NGS] is an acceptable alternative)**
  - **Consider programmed death ligand 1 (PD-L1) IHC for patients with recurrent, progressive, or metastatic disease**
  - **HER2 IHC (with or without reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) is recommended for advanced or recurrent/metastatic disease**
  - **Consider comprehensive molecular profiling by an FDA-approved assay, or a validated test performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory including at least microsatellite instability (MSI), tumor mutational burden (TMB) testing, *NTRK*, and *RET* for predicting rare pan-tumor targeted therapy opportunities**
  - **Mismatch repair (MMR) by IHC**

[a] p16 expression has been noted in a subset of HPV-independent vaginal squamous cell carcinomas.

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PRINCIPLES OF IMAGING[a]

Workup

- **Pelvis MRI and vaginal gel to assess local disease extent (preferred).**
- **Neck/chest/abdomen/pelvis/groin fluorodeoxyglucose (FDG)-PET/CT (preferred) or chest/abdomen/pelvis CT to evaluate for metastatic disease.**
- **Other initial imaging should be based on symptomatology and clinical concern for metastatic disease.**

Follow-up

- **FDG-PET/CT (preferred) at 3–4 months after RT.**
- **MRI if unable to obtain FDG-PET/CT or needed for clarification of FDG-PET/CT or exam findings.**
- **Repeat imaging if clinically indicated.**

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

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PRINCIPLES OF RADIATION[1-8]

General Principles

- For the majority of vaginal cancers, radiation is used rather than surgery as primary treatment due to improved organ preservation. Preferred modalities for definitive management include either concurrent pelvic chemoradiation (platinum-based) + brachytherapy or EBRT + brachytherapy. The addition of brachytherapy to EBRT is preferred as the combination has been shown to improve control.
- Overall treatment time should not extend beyond 8 weeks.
- Treatment delays/interruptions need to be minimized.

External Beam Radiation Therapy/Intensity Modulated Radiation Therapy (EBRT/IMRT)

- Simulation
  - IMRT
    - ◊ Simulate and treat supine, frog-legged with custom immobilization when including the groin, with full bladder. Consider bladder full and empty CT scans to generate vaginal internal organ motion (internal target volume [ITV]).
    - ◊ Consider oral and IV contrast.
    - ◊ Place markers at tumor for delineation and fuse with MRI/PET imaging (if available) to define tumor extent.
    - ◊ Consider placement of vaginal gel during MRI for additional delineation of intraluminal disease.

- Dose Prescription
  - IMRT
    - ◊ 45–50 Gy in 1.8–2.0 Gy/fraction
    - ◊ For gross nodes, consider simultaneous integrated or sequential boost to 55–70 Gy equivalent dose at 2 Gy (EQD2).
    - ◊ If the primary lesion was resected surgically with close or positive margins and EBRT boost is planned, dose is 54–60 Gy to the postoperative bed. Alternatively a brachytherapy boost can be given.

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References

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All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION[1-8]

External Beam Radiation Therapy/Intensity Modulated Radiation Therapy (EBRT/IMRT) continued

- **Target Delineation[a]**
  - Gross tumor volume (GTV) primary = Primary tumor delineated by exam (including EUA) and fusion with MRI and/or FDG-PET/CT.
  - Clinical target volume (CTV) primary = Entire vagina, paravaginal tissues, cervix, parametria, and GTV with 1- to 2-cm margin. Account for possible ITV as vaginal apex can move up to 2 cm in anterior-posterior (AP) direction. To develop an ITV, patients should be simulated with full and empty bladder. CTVs from both scans should be combined to create an ITV. If there is involvement of adjacent organs (ie, urethra or rectum), consider their inclusion in CTV.
  - CTV nodes = Pelvic nodal coverage of common iliac, internal and external iliac, presacral, and obturator nodes, and if lower third of vagina involved include inguinal nodes. Include para-aortic nodes if common iliac/para-aortic nodes involved. Include pelvic vessels with 7-mm expansion excluding bone/muscle/organs. Tumors involving the posterior vaginal wall and recto vaginal septum have an increased risk of spread to the presacral and mesorectal nodes; inclusion of the entire mesorectum should be considered in these cases.
  - Inguinofemoral node borders for distal vaginal cases: superior = acetabular roof; lateral = inguinofemoral vessels to medial sartorius/rectus femoris; posterior = posterior border of vessels; medial = pectineus muscle or 2.5–3 cm from vessels; anterior = anterior border of sartorius; caudal = top of lesser trochanter of femur.
  - Planning target volume (PTV) expansion 0.5–0.7 cm from CTV per institutional required margin to account for setup error based on image verification available.
  - Inferior field border should extend approximately 3 cm below the inferior extent of vaginal disease.

- **Planning/Treatment**
  - EBRT
    - IMRT is used as a treatment technique to spare organs at risk (OAR). Attention should be given to internal target motion in planning.
    - Consider treatment with full bladder to minimize bowel dose.
    - A minimum of weekly portal images; daily image-guided RT (IGRT) is advised, especially if IMRT is utilized.
    - Bolus may be necessary to adequately cover inguinal nodes.

[a] For further details, refer to GEC-ESTRO recommendations.[6,8]

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Continued

References

PRINCIPLES OF RADIATION[1-8]

Brachytherapy

- Simulation
  - Intracavitary applicator (for ≤5-mm gross disease thickness)
    - May be done with single channel, multichannel (Miami applicator), or partially shielded vaginal cylinder applicators
  - Interstitial needles (>5-mm gross disease thickness)—perineal template applicator (ie, Syed), hybrid, or freehand; consider referral to treatment center with specialist/expertise
  - Real-time image guidance with CT, MRI, or transrectal ultrasound (US)
- Dose Prescription
  - Brachytherapy to reach 70–80 Gy EQD2 total dose (alpha/beta [α/β] ratio = 10) to high-risk CTV (HR-CTV) is generally recommended, with lower dose ranges of 70–75 Gy considered in the lower vagina, and 75–80 Gy total dose in the upper vagina. For bulky or poorly responsive disease in the upper vagina, dose escalation up to 85 Gy may be considered. Some treat entire vaginal surface to 60 Gy cumulative, followed by tumor boost to 70–80 Gy, while others treat only the lesion plus a margin. Careful attention should be paid to dose tolerance of vaginal mucosa. The distal vagina has a lower tolerance than the proximal vagina.
  - For invasive cancers, common high dose-rate (HDR) fractionation regimens after 45 Gy to pelvis include 4.5–5.5 Gy x 5 fractions to the HR-CTV. Either less fractionated or more fractionated regimens may be used, such as 7 Gy x 3 fractions or 3 Gy x 9–10 fractions. Modulation of dose takes into consideration tumor location, extent of disease, response to EBRT, brachytherapy technique (intracavitary or interstitial), relationship to surrounding OARs, as well as other factors.
  - For very-early-stage vaginal cancers (<5 mm) not requiring EBRT, intracavitary brachytherapy alone may be used. Low dose-rate (LDR) data suggest improved outcomes with doses of approximately 60–70 Gy EQD2 to the vaginal surface. The HDR data are more varied, with total doses in the range of 50–60 Gy EQD2. The appropriate dose for each case needs to be individualized. Common regimens include 5 Gy x 8 fractions or 8 Gy x 5 fractions to the vaginal surface, with treatments delivered twice per week.
- Dose Constraints: See (VAG-C 5 of 7)
- Target Delineation[a]
  - Brachytherapy planning is highly individualized and should incorporate information from pre-EBRT and pre-brachytherapy imaging (preferably MRI), clinical drawings, fiducials, and exam findings. Careful understanding of vaginal anatomy and distribution of disease is required. Image-guided brachytherapy is strongly encouraged, with adaptation of volumes as tumor responds. Tumor extent, location, and response must all be considered when choosing the brachytherapy approach.
  - GTV: macroscopic gross residual tumor at time of brachytherapy by imaging and clinical exam
  - HR-CTV: GTV + any abnormal/irregular vaginal wall within initial tumor extension + paravaginal/parametrial gray zones (if applicable)
- Planning/Treatment
  - IGRT adaptive planning encouraged
  - Attention to vaginal surface dose and surrounding dose to OARs
  - Use biologically effective dose (BED) dose conversions to track EQD2 dose to normal tissues (α/β ratio = 3) and to vaginal target/HR-CTV (α/β ratio = 10)

[a] For further details, refer to GEC-ESTRO recommendations.[6,8]

Continued
References

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PRINCIPLES OF RADIATION[1-8]

External Beam Boost

- Although brachytherapy is typically preferred, a carefully designed IMRT boost may be feasible in place of brachytherapy, if a similar EQD2 can be achieved without significant increased dose to the OARs. In such cases, total dose should aim for 65–70 Gy.
- This may be appropriate for patients who are poor candidates for brachytherapy or where concern for toxicity is high, such as tumors that are extremely close to the rectum or anus.

Reirradiation

- IORT (category 3): IORT is a specialized technique that delivers a single, highly focused dose of radiation to an at-risk tumor bed or isolated unresectable residual disease during an open surgical procedure.[5] It is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such as bowel or other viscera) can be manually displaced from the region at risk. IORT is typically delivered with electrons, brachytherapy, or miniaturized x-ray sources using preformed applicators of variable sizes matched to the surgically defined region at risk, which further constrains the area and depth of radiation exposure to avoid surrounding normal structures.
- Other techniques for reirradiation may include intracavitary or interstitial brachytherapy, SBRT, IMRT, or proton therapy. Such cases are highly individualized and depend on the target, proximity to critical organs, previous RT dose, extent of overlap, and time intervals since prior RT. The appropriate dose for each case needs to be individualized.

Continued
References

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION[1-8]

NORMAL TISSUE DOSE CONSTRAINT GUIDELINES FOR VAGINAL CANCER[9-11]

Organs at Risk	Dose Recommendation	
EBRT	**Soft Constraint**	**Hard Constraint**
Bowel	≤30% receives 40 Gy	≤70% receives 40 Gy
	V45 ≤200 cc	V45 <250 cc
	For nodal boost: V55 <5 cc	For nodal boost: V55 <15 cc
Bladder[b]	V45 <50%	Dmax <57.5 Gy
Anorectum[b]	V45 <50% V30 <60%	Dmax <57.5 Gy
Femoral Heads[b]	V30 <15%	Dmax <55 Gy
Bone Marrow (optional)	V10 <80% V20 <66%	V10 <90% V20 <75%
Spinal Cord	Dmax ≤45 Gy	—
External Genitalia[c]	V40 <5% V30 <35% V35 <50%	—

[b] In cases where an EBRT boost is used, vulvar constraints may be appropriate: Bladder: Dmax <65 Gy; Anorectum: Dmax <65 Gy; and Femoral heads: Dmax <55 Gy.
[c] Care should be taken to minimize dose to uninvolved and out-of-field external genitalia when possible but without compromising coverage of the PTV.

Continued
References

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION[1-8]

NORMAL TISSUE DOSE CONSTRAINT GUIDELINES FOR VAGINAL CANCER[9-11]

Brachytherapy (including EBRT dose contribution)			
Organs at Risk	**Ideal Dose Constraint (Gy) ($EQD2_3$)**	**Maximum Dose Constraint (Gy) ($EQD2_3$)**	**ICRU Point (Gy) ($EQD2_3$)**
Rectum	<65 D2 cc	<75 D2 cc	<65 point dose
Bladder	75–80 D2 cc	<90 D2 cc	<75 point dose
Sigmoid	<70 D2 cc	<75 D2 cc	—
Bowel	<70 D2 cc	<75 D2 cc	—
Urethra	0.1 cc less than prescription dose (estimated EQD2 of 85 Gy)	—	—

Clinicians must balance the risks of normal tissue toxicity with tumor control, but suggested dose constraints are provided. Studies indicate that 20%–30% of cases may not meet every constraint.

References

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION
REFERENCES

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Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

SYSTEMIC THERAPY FOR PRIMARY VAGINAL CANCER (REGIMENS ARE EXTRAPOLATED FROM CERVICAL CANCER)[a,b,c]

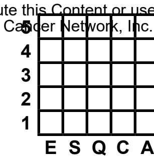
Squamous Cell Carcinoma, Adenocarcinoma		
Chemoradiation[d]	**Recurrent or Metastatic Disease**	
	First-Line Therapy[d,e]	**Second-Line or Subsequent Therapy[e]**
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant **Other Recommended Regimens (if cisplatin and carboplatin are unavailable)** • Capecitabine/mitomycin[1] • Gemcitabine[2] • Paclitaxel[3,4]	**Preferred Regimens** • PD-L1–positive tumors ▸ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab[f,g,h,5] ▸ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab[f,g,h,5] • Cisplatin/paclitaxel/bevacizumab[h,6] • Carboplatin/paclitaxel/bevacizumab[h,6] **Other Recommended Regimens** • Cisplatin/paclitaxel[7,8] • Carboplatin/paclitaxel[9,10] • Topotecan/paclitaxel/bevacizumab[h,6,11] • Topotecan/paclitaxel[11] • Cisplatin/topotecan[11] • Cisplatin[8] • Carboplatin[12,13]	**Preferred Regimens** • Pembrolizumab[f] for TMB-high (TMB-H) tumors[i] or PD-L1–positive[g] or MSI-H/mismatch repair deficient (dMMR) tumors[14] **Other Recommended Regimens** • Bevacizumab • Paclitaxel[13,15] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan • Tisotumab vedotin-tftv[16] • Cemiplimab[f,17] **Useful in Certain Circumstances** • PD-L1–positive tumors ▸ Nivolumab[f,g,j,18] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[19] • *RET* gene fusion-positive tumors ▸ Selpercatinib • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib ▸ Repotrectinib[k,20]

See Evidence Blocks on VAG-D (EB-1) and VAG-D (EB-2)

Footnotes on VAG-D 1A of 2

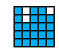
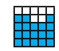
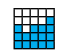
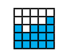
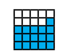
Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

References



EVIDENCE BLOCKS FOR CHEMORADIATION AND SYSTEMIC THERAPY

(VAG-D [1 of 2])

SQUAMOUS CELL CARCINOMA, ADENOCARCINOMA	
CHEMORADIATION	
Preferred Regimens	
Cisplatin	
Carboplatin	
Other Recommended Regimens (if cisplatin and carboplatin are unavailable)	
Capecitabine/mitomycin	
Gemcitabine	
Paclitaxel	

Continued

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

EVIDENCE BLOCKS FOR CHEMORADIATION AND SYSTEMIC THERAPY
(VAG-D [1 of 2])

SQUAMOUS CELL CARCINOMA, ADENOCARCINOMA

RECURRENT OR METASTATIC DISEASE

FIRST-LINE THERAPY	
Preferred Regimens	
Pembrolizumab + cisplatin/paclitaxel (PD-L1–positive tumors)	
Pembrolizumab + cisplatin/paclitaxel + bevacizumab (PD-L1–positive tumors)	
Pembrolizumab + carboplatin/paclitaxel (PD-L1–positive tumors)	
Pembrolizumab + carboplatin/paclitaxel + bevacizumab (PD-L1–positive tumors)	
Cisplatin/paclitaxel/bevacizumab	
Carboplatin/paclitaxel/bevacizumab	
Other Recommended Regimens	
Cisplatin/paclitaxel	
Carboplatin/paclitaxel	
Topotecan/paclitaxel/bevacizumab	
Topotecan/paclitaxel	
Cisplatin/topotecan	
Cisplatin	
Carboplatin	

SECOND-LINE OR SUBSEQUENT THERAPY	
Preferred Regimen	
Pembrolizumab (TMB-high or PD-L1-positive or MSI-H/dMMR tumors)	
Other Recommended Regimens	
Bevacizumab	
Paclitaxel	
Albumin-bound paclitaxel	
Docetaxel	
Fluorouracil	
Gemcitabine	
Pemetrexed	
Topotecan	
Vinorelbine	
Irinotecan	
Tisotumab vedotin-tftv	
Cemiplimab	

Useful in Certain Circumstances	
Nivolumab (PD-L1–positive tumors)	
Fam-trastuzumab deruxtecan-nxki (HER2-positive tumors)	
Selpercatinib (RET gene fusion-positive tumors)	
Larotrectinib (*NTRK* gene fusion-positive tumors)	
Entrectinib (*NTRK* gene fusion-positive tumors)	
Repotrectinib (*NTRK* gene fusion-positive tumors)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

FOOTNOTES FROM VAG-D 1 OF 2

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[b] The majority of cases in the vagina might be arising from another site. In these cases, one should refer to the corresponding NCCN Treatment Guidelines.
[c] Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions. See NCCN Guidelines for Ovarian Cancer–Management of Drug Reactions (OV-D).
[d] Toxicity, especially when using extended-field RT, should be carefully considered when selecting an appropriate regimen for treatment.
[e] If not used previously, these agents can be used as second-line or subsequent therapy as clinically appropriate.
[f] NCCN Guidelines for the Management of Immunotherapy-Related Toxicities.
[g] Recommended in patients whose tumors express PD-L1 (combined positive score [CPS] ≥1).
[h] Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.
[i] For the treatment of patients with unresectable or metastatic TMB-H [≥10 mutations/megabase (mut/Mb)] tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.
[j] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[k] *NTRK*-positive tumors that are naïve to prior *NTRK* targeted therapy or have progressed on prior *NTRK* therapy.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

SYSTEMIC THERAPY FOR VAGINAL CANCER
REFERENCES

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Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SURGERY

Initial Diagnosis:
- **Patients should be evaluated by a gynecologic oncologist prior to any surgical treatment for vaginal cancer.**
- **Surgery is only recommended if a complete resection with clear margins is feasible without excessive morbidity and with likelihood that no adjuvant RT would be required.**
- **EUA may be helpful to confirm diagnosis, obtain adequate tissue sampling for histologic evaluation and comprehensive molecular profiling such as PD-L1, and assess the extent of disease. Consider cystoscopy and proctoscopy concurrently to exclude bladder/rectal invasion. Perform evaluation of cervix and vulva to exclude other gynecologic primary sites.**
- **In patients who are premenopausal, ovarian preservation or transposition should be considered when feasible.**
- **Fiducial markers may be placed to define the extent of the vaginal lesion.**
- **Definitive surgical management for vaginal cancer is not often utilized, and the alternative of radiation should be considered.**
- **For microscopic lesions at the top of the vagina, upper vaginectomy ± hysterectomy may be reasonable. A radical hysterectomy may be appropriate for macroscopic lesions (<2 cm).**
- **For proximal lesions involving the upper two thirds of the vagina, the pelvic lymph nodes should be assessed.**
- **For distal lesions involving the lower 1/3 of the vagina, the inguinal lymph nodes should be assessed.**
- **Vaginal reconstruction should be considered for appropriate candidates desiring such procedures.**
- **For primary, untreated lesions in which resection would require excision of the urethra, bladder, or rectum, radiation is often preferred.**
- **Vaginectomy may be considered for small lesions for which margins are likely to be negative. Every effort should be made to obtain negative margins.**
- **Pelvic exenteration may be considered for recurrent or persistent disease localized to the pelvis or when primary RT is not feasible.**

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF GYNECOLOGIC SURVIVORSHIP

Physical Effects
- Gynecologic cancer treatment typically involves surgery, chemotherapy, hormone therapy, RT, and/or immunotherapy. These treatments cause acute, short-term, and long-term toxicities.
- Surgical approaches may be extensive and pose risks such as adhesion formation, which may cause pain and may contribute to small bowel obstruction, urinary or gastrointestinal complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a variety of urinary, bowel, and/or sexual effects), and lymphedema.
- Chemotherapy agents vary, though 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. Local vaginal estrogen may be considered if symptomatic.
- For treatment-related menopause, hormone therapy should be considered.
- Communication and coordination with all clinicians involved in the care of survivors, including primary care clinicians, is critical. Providing cancer survivors with a summary of their treatment and recommendations for follow-up is recommended.

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

Table 1. AJCC Tumor, Node, Metastasis (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Carcinoma of the Vagina

T	FIGO Stage	Primary Tumor
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	**I**	Tumor confined to the vagina
T1a	**I**	Tumor confined to the vagina, measuring ≤2.0 cm
T1b	**I**	Tumor confined to the vagina, measuring >2.0 cm
T2	**II**	Tumor invading paravaginal tissues but not to pelvic sidewall
T2a	**II**	Tumor invading paravaginal tissues but not to pelvic wall, measuring ≤2.0 cm
T2b	**II**	Tumor invading paravaginal tissues but not to pelvic wall, measuring >2.0 cm
T3	**III**	Tumor extending to the pelvic sidewall* and/or causing hydronephrosis or nonfunctioning kidney
T4	**IVA**	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)

*Pelvic sidewall is defined as the muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall.

N	FIGO Stage	Regional Lymph Nodes
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	**III**	Pelvic or inguinal lymph node metastasis

M	FIGO Stage	Distant Metastasis
M0		No distant metastasis
M1	**IVB**	Distant metastasis

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

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and from: FIGO Committee on Gynecologic Oncology. Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. Int J Gynaecol Obstet 2009;105:3-4. Copyright 2009, with permission from International Federation of Gynecology and Obstetrics.

AFAB assigned female at birth
AP anteroposterior

BED biologically effective dose
BUN blood urea nitrogen

CBC complete blood count
CLIA Clinical Laboratory Improvement Amendments
CMP comprehensive metabolic panel
CPS combined positive score
CTV clinical target volume

dMMR mismatch repair deficient

EBRT external beam radiation therapy
EQD2 equivalent dose at 2 Gy
EUA examination under anesthesia

FDG fluorodeoxyglucose
FISH fluorescence in situ hybridization

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

NCCN Guidelines Version 5.2025
Vaginal Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Vaginal Cancer (V.5.2025). Last updated on February 28, 2025.

Table of Contents

Overview

Vaginal cancer is a rare gynecologic malignancy representing 1% to 2% of all gynecologic neoplasms.[1] An estimated 8070 new cases of vaginal and other genital cancers will be diagnosed in the United States in 2025, and 1950 people are estimated to die of the disease.[2] Because of the rarity of vaginal cancer, phase 3 trials have not been carried out and current guidelines have been drawn up on retrospective or comparative studies. Vaginal cancer is also the most common type of metachronous malignancy after cervical cancer diagnosis, followed by vulvar cancer and anal cancer.[3] In individuals with cervical intraepithelial neoplasia at the time of hysterectomy, the risk of contracting vaginal cancer is more than double compared to non-hysterectomized individuals[4]. The risk for vaginal cancers is most common in individuals AFAB >70 years. Age-standardized incidence rate of vaginal preinvasive neoplasia ranges between 0.5 to 1.3 per 100,000 individuals AFAB (before human papillomavirus [HPV] vaccination) and those aged 60 to 69 years are at greater risk.[5] The majority of invasive vaginal carcinomas are squamous cell carcinoma (SCC), and the second most common type is melanoma.[6] SCC accounts for 80% to 90% of cases and most commonly arises in the upper portion of the posterior wall of the vagina.[6] Some of the risk factors based on etiologic insights from case studies include vaginal damage from ring pessaries, chronic vaginitis, sexual behavior, birthing trauma, obesity, exposure to chemicals in the vagina, and HPV.[7]

Persistent infection with high-risk HPV types has been detected in 40% to 70% of all vulvar and vaginal cancers, and in about 85% to 90% of vaginal intraepithelial neoplasia grades 2 and 3 (VaIN 2/3).[5] The specific HPV types detected in cervical, vulvar, and vaginal cancer vary widely due to differences in the sensitivity of the HPV detection methods used, HPV distribution, and different HPV positivity age groups reported. HPV16, the most common type, is detected in 48% to 72% of cervical, 27% to 58% of vulvar, and 46% to 77% of vaginal cancers. HPV18 has been detected in 11% to 22% of cervical, 2% to 10% of vulvar, and 3% to 27% of vaginal cancers. HPV16 has been reported to be present in 49% to 81% of VaIN 2/3, whereas only 2% to 14% of these lesions test positive for HPV18.[5]

Since patients with previous cervical carcinoma have a substantial risk of developing vaginal carcinoma, presumably because these sites share exposure and/or susceptibility to endogenous or exogenous carcinogenic stimuli, epidemiologic risk factors associated with cervical cancer are also shared risk factors for vaginal cancer including history of smoking, parity, oral contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease, certain autoimmune diseases, and chronic immunosuppression.[8-10] Smoking cessation should be advised in patients who currently smoke, and patients who formerly smoked should continue to avoid smoking (see the NCCN Guidelines for Smoking Cessation and http://smokefree.gov).

In 2020, the World Health Organization (WHO) updated the Female Genital Tumors classification and recommends distinguishing between HPV-associated and HPV-independent SCC of the vagina.[11] The majority of vaginal SCCs are HPV-associated with a non-keratinizing morphology and are in the proximal or intermediate third (Müllerian) portion of the vagina. Distal SCCs, also known as introitus carcinoma and that stem from the urogenital sinus, generally lack HPV association and are often keratinizing SCCs.[11] WHO recommends that for vaginal carcinomas, molecular analyses (ie, HPV detection in situ) are not indicated for the diagnostic evaluation.

The NCCN Vaginal Cancer Guidelines subcommittee acknowledges that the 2020 version of the WHO classification discussed the integration of the immunohistochemical (IHC) and molecular profiles that has led to a better classification system that is now adapted in the 2020 WHO Classification of Female Genital Tumors.[11]

Regardless of cancer subtype and HPV infection status, primary treatment with curative intent for patients with vaginal cancer typically consists of radiation, surgery, chemoradiation, or a combination of these treatments; options vary by cancer stage. By definition, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. “Many exceptions to the rule” were discussed among the members of the Vaginal Cancer Panel during the process of developing these Guidelines.

Guidelines Update Methodology

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

Literature Search Criteria

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

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Randomized Controlled Trial; Meta-Analysis; Multi-center studies; Systematic Reviews; and Validation Studies.

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

Sensitive/Inclusive Language Usage

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

Diagnosis and Workup

The most significant signs of vaginal cancer are bleeding, discharge, urine retention and rectal symptoms such as constipation or blood in the stool. However, up to 20% of individuals AFAB may be asymptomatic and have the disease discovered on pelvic (bimanual and rectovaginal) or cervical examination and pap cytology, colposcopy, or vulvar screening. Cofactors for vaginal cancer include immunosuppression, prior hysterectomy, and cigarette smoking. As a synchronous or metachronous tumor, vaginal

cancer is frequently found in combination with cervical cancer. With a rare cancer like vaginal cancer, it is important to consider synchronous anorectal, cervical, endometrial, or vulvar primary with vaginal metastasis or extension, or recurrent disease from prior malignancy. Only a minority of vaginal cancers originate in the vagina. The remaining are generally metastatic from other sites. If vaginal lesion(s) involve the cervix or vulva, they are not considered vaginal cancer, and the appropriate treatment algorithm should be consulted. Biopsy remains the gold standard for diagnosing vaginal cancer. This can be best accomplished by an examination under anesthesia (EUA) and should include inspection of the vaginal fornices and biopsies of the cervix.

Workup for these patients with suspicious symptoms includes history and physical, pelvic exam (bimanual and rectovaginal), cervical evaluation and pap cytology, colposcopy, vulvar evaluation, imaging, complete blood count (CBC), comprehensive metabolic panel (CMP), and testing for HPV and human immunodeficiency virus (HIV) in select patients. Due to diverse diagnosis of vaginal cancer, multidisciplinary expertise is recommended.

For detailed surgical staging and imaging recommendations by stage and planned treatment approach, see *Principles of Surgery*, *Principles of Imaging*, and *Staging* in the algorithm. Smoking cessation and counseling, as well as HIV testing (especially in younger patients), are recommended.

Principles of Staging and Surgery

Clinical Staging

Vaginal cancer is primarily staged clinically like cervical cancer. The staging is based on the results of a physical exam, biopsy, and imaging tests performed before treatment selection using 2009 International Federation of Gynecology and Obstetrics (FIGO) staging. The FIGO Gynecologic Oncology Committee also recommends that imaging should be used to better define tumor volume and extension of disease wherever available.

The staging definition according to FIGO 2009 staging is as follows: stage IA, the cancer is only in the vagina and is ≤2.0 cm; stage IB, the tumor is confined to the vagina, measuring >2.0 cm; stage IIA, the cancer has grown through the vaginal wall, but not as far as the pelvic wall and is ≤2.0 cm (4/5 inch); stage IIB, the cancer has grown through the vaginal wall, but not as far as the pelvic wall and is >2.0 cm (4/5 inch); stage III, the tumor extends to the pelvic sidewall (defined as the muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis) and/or is causing hydronephrosis or nonfunctioning kidney; stage IVA, the tumor is invading the mucosa of the bladder or rectum and/or is extending beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4); and stage IVB, distant metastasis.

Principles of Pathology

Pathologic Assessment

The College of American Pathologists (CAP) protocol for primary carcinoma of the vagina is a useful guide for the examination of resection specimens: https://documents.cap.org/protocols/cp-femalereproductive-vagina-resection-20-4201.pdf.

This CAP protocol was revised in February 2020 and reflects recent updates to AJCC staging (ie, AJCC Cancer Staging Manual, 8th edition) and FIGO Cancer Report 2018.[12] All staging guidelines in the algorithm are based on 2009 FIGO staging and AJCC staging, unless otherwise noted. Surgico-pathologic factors may be used to guide the extent of surgical staging and treatment decisions. Findings from pathologic assessment of the surgical specimen should be carefully documented according to CAP protocol for vaginal carcinoma. Important elements of primary tumor evaluation include the procedure type (ie, biopsy, local

excision, partial vaginectomy, radical vaginectomy, trachelectomy); tumor site (upper, middle, or lower third); tumor size to include greatest dimension and additional two dimensions; histologic types that include HPV-associated SCC, HPV-independent SCC, HPV-associated vaginal adenocarcinoma, endometrioid carcinoma, and clear cell carcinoma; histologic grade (well, moderately, and poorly differentiated); lymphovascular space invasion (LVSI); precursor lesions (VaIN/squamous intraepithelial lesion [SIL]); determination of primary site; and surgical resection margin status.

General Principles

Vaginal carcinomas account for <1% of cancers affecting individuals AFAB worldwide. The predominant pathway for vaginal SIL and vaginal SCC is HPV infection-predominant high-risk HPV types with the most common type being HPV16. In 2012, based on the recommendation of the Lower Anogenital Squamous Terminology (LAST) Project, a uniform two-tiered terminology for HPV-associated SIL across all anogenital tract organs that distinguishes between low-grade SIL (LSIL) and high-grade SIL (HSIL) was introduced.[13] SIL is now the preferred terminology, which can be synonymously used with the three-tiered system of intraepithelial neoplasia. LSIL encompasses both low- and high-risk HPV infection and VaIN 1, while HSIL includes VaIN 2 and VaIN 3 and is exclusively associated with high-risk HPV types.[14] The risk of progression from HSIL or VaIN to invasive SCC is approximately 5%. Categorization of vaginal SCC has been simplified into HPV-associated and HPV-independent types based upon pathogenesis. If association is unknown, inclusion of “not otherwise specified (NOS)” is recommended. Previously used terms, “warty,” “basaloid,” “verrucous,” and “papillary,” are no longer necessary components of the histologic type. HPV-independent SCCs of the vagina are much less common and are often seen in postmenopausal individuals AFAB (median age 73 years). These tumors are predominantly of the keratinizing type of histology and demonstrate negative p16 and positive p53 IHC. As with HPV-associated vaginal carcinomas, prior history (<5 years) of cervical and vulvar carcinomas must be excluded.

Other types of vaginal carcinomas are very rare and include HPV-associated vaginal adenocarcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma (gastric and intestinal types), mesonephric adenocarcinoma, carcinosarcoma, mixed tumor of the vagina, adenocarcinoma of skene gland origin, adenosquamous carcinoma, adenoid basal carcinoma, neuroendocrine carcinomas, adenosarcoma, and germ cell tumors.

Next-generation sequencing (NGS) and comprehensive molecular profiling as determined by a U.S. Food and Drug Administration (FDA)-approved assay, or validated test performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory is recommended for the following biomarkers: programmed cell death ligand 1 (PD-L1), microsatellite instability-high (MSI-H), tumor mutational burden (TMB), *NTRK* fusion, *RET* fusion, HER2 IHC or fluorescence in situ hybridization (FISH), and p53 IHC.

Prognostic and Predictive Biomarkers

The data cited within this section are primarily for cervical cancer and have been generalized to vaginal cancer. Because of the uncommon nature of vaginal cancer and its similarities to cervical cancer, many of the treatment recommendations are derived from those for cervical cancer. Several biomarker-based immune-oncologic agents have been added from the NCCN Guidelines for Cervical Cancer to the NCCN Guidelines for Vaginal Cancer in the management of vaginal cancer (see *Systemic Therapy Recommendations*) and the NCCN Panel recommends comprehensive molecular profiling as determined by an

FDA-approved assay, or a validated test performed in a CLIA-certified laboratory.

PD-L1

The NCCN Panel recommends PD-L1 testing by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory for patients with recurrent, progressive, or metastatic disease to help guide better treatment options in first-line, second-line, or subsequent therapy.[15]

The FDA approved pembrolizumab plus chemotherapy, with or without bevacizumab, for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (combined positive score [CPS] ≥1) based on the KEYNOTE-826 study.[15] The NCCN Panel also recommends this regimen as a preferred regimen (category 1) for first-line therapy for recurrent or metastatic vaginal cancer.

KEYNOTE-158 is another phase 2 basket study that evaluated the use of pembrolizumab in multiple cancer types including cervical cancer.[16] The interim results from previously treated patients with advanced cervical cancer demonstrated the durable antitumor activity and manageable safety of pembrolizumab monotherapy. Out of 98 patients treated, 82 (83.7%) had PD-L1–positive tumors (CPS ≥1), with 77 having previously received one or more lines of chemotherapy for recurrent or metastatic disease. The primary endpoint, overall response rate (ORR), was 12.2% (95% CI, 6.5%–20.4%), with 3 complete and 9 partial responses (PRs). All 12 responses were in patients with PD-L1–positive tumors, for an ORR of 14.6% (95% CI, 7.8%–24.2%); 14.3% (95% CI, 7.4%–24.1%) of these responses were in those who had received one or more lines of chemotherapy for recurrent or metastatic disease. Based on these results, the FDA granted accelerated approval of pembrolizumab for patients with advanced PD-L1–positive cervical cancer who experienced progression during or after chemotherapy. NCCN also recommends pembrolizumab as a preferred regimen for patients who are PD-L1–positive for second-line or subsequent therapy for vaginal cancer, based on the recommendations for cervical cancer.

Nivolumab, a checkpoint inhibitor, has shown efficacy in patients with recurrent/metastatic cervical cancer who received at least one prior chemotherapy regimen. The Checkmate-358, phase 1–2, single-arm trial evaluated 19 patients with advanced, pretreated, HPV-associated cervical tumors.[17] The ORR was 26.3% (95% CI, 9.1%–51.2%) and disease control rate was 68.4% (95% CI, 43.4%–87.4%). The 12-month overall survival (OS) rate was 77.5% (95% CI, 50.5%–91.0%). The phase 2 trial (NRG-GY002) showed low anti-tumor activity of nivolumab in 25 patients with pretreated persistent/recurrent cervical cancer; 36% of the patients had stable disease (90% CI, 20.2%−54.4%) as best response with median duration of 5.7 months, and progression-free survival (PFS) and OS at 6 months were 16% and 78.4%, respectively.[18,19]

Based on the NCCN Guidelines for Cervical Cancer, the Panel continues to recommend nivolumab in the same category of “useful in certain circumstances” for second-line or subsequent therapy for vaginal cancer. Following FDA approval[20] of nivolumab and hyaluronidase for subcutaneous injection across approved adult solid tumor as monotherapy, and monotherapy maintenance following completion of nivolumab, the NCCN Panel added that nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

Mismatch Repair/Microsatellite Instability

Tumors with mismatch repair deficiency (dMMR) represent approximately 2% to 4% of all diagnosed cancers and have a unique genetic signature, harboring 10 to 100 times more mutations than

mismatch repair–proficient tumors. These dMMR tumors have MSI-H and harbor 100 to 1000 somatic mutations that encode potential neoantigens and are likely to be immunogenic. The KEYNOTE-158 trial included patients with non-colorectal MSI-H/dMMR tumors in cohort K and the results demonstrated the clinical benefit of pembrolizumab in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer.[21]

Of 233 patients with MSI-H/dMMR advanced non-colorectal cancer whose disease progressed on prior therapy received pembrolizumab, the ORR was 34.3% (95% CI, 28.3%–40.8%). Median PFS was 4.1 months (95% CI, 2.4–4.9 months) and median OS was 23.5 months (95% CI, 13.5 months – not reached[NR]). Extending the NCCN Panel recommendation for cervical cancers, pembrolizumab is also recommended as a preferred regimen for MSI-H/dMMR tumors as a second-line or subsequent therapy for recurrent or metastatic vaginal cancer.

TMB

TMB, defined as the total number of somatic mutations per coding area of a tumor genome, is a measure of all non-synonymous coding mutations in a tumor exome; highly mutated tumors can produce many neoantigens, some of which might increase T-cell reactivity. High TMB has been demonstrated to be associated with treatment response to pembrolizumab.

In a prospective analysis of the multi-cohort, open-label, non-randomized phase 2 KEYNOTE-158 study,[22] the association between antitumor activity and tissue TMB (tTMB) in patients who received at least one dose of pembrolizumab was assessed and tTMB-high (tTMB-H) status identified a subgroup of patients who could have a robust tumor response to pembrolizumab monotherapy. Out of 790 TMB-evaluable, treated patients enrolled by at least 26 weeks before data cutoff, 102 (13%) patients were tTMB-H (<10 mutations per megabase [mut/Mb]) and 688 (87%) patients had non–tTMB-H status. With a median study follow-up of 37.1 months, the objective responses were observed in 30 (29%; 95% CI, 21–39) of 102 patients in the tTMB-H group and 43 (6%; 95% CI; 5–8) of 688 patients in the non–tTMB-H group. Cervical cancer had the highest proportion of patients with tTMB-H status (21%) and objective responses were observed in 5 of 16 patients with tTMB-H status and 7 of 59 patients with non–tTMB-H status within the cervical cohort.

The NCCN Panel recommends TMB testing by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory and recommends pembrolizumab as a preferred regimen for the treatment of patients with TMB-high (TMB-H) (≥10 mut/Mb) tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options (second-line or subsequent therapy).

NTRK Gene Fusion

NTRK gene fusions are found in about 1% of all solid tumors. An integrated efficacy and safety analysis of patients with metastatic or locally advanced solid tumors harboring oncogenic *NTRK1*, *NTRK2*, and *NTRK3* gene fusions treated with entrectinib in three ongoing, early-phase trials (ALKA-372–001, STARTRK-1, and STARTRK-2) showed durable and clinically meaningful responses with manageable safety profile.[23] The efficacy-evaluable population comprised 54 adults with advanced or metastatic *NTRK* fusion-positive solid tumors comprising 10 different tumor types and 19 different histologies, including one patient with cervical sarcoma. Out of 54 patients, 31 (57%; 95% CI, 43.2–70.8) had an objective response, of which 4 (7%) were complete responses (CRs) and 27 (50%) were PRs. Median duration of response (DoR) was 10 months (95% CI, 7.1 – not estimable [NE]). In a long-term efficacy and safety analysis in 121 patients at median follow-up of 25.8

months, 61% reported CRs or PRs, median DoR was 20 months (95% CI, 10.1–19.9), and median PFS was 13.8 months (95% CI, 10.1–19.9).[24]

In another primary analysis, the efficacy and safety of larotrectinib was reported in 55 patients enrolled in three clinical studies who had locally advanced or metastatic tumors with *NTRK* gene fusions and had progressed on standard chemotherapy received previously. The three clinical trials included a phase 1 dose-finding study in adults, a phase 1–2 dose-finding study in a pediatric population, and a phase 2, single-arm, basket trial.[25] The ORR of larotrectinib in these patients was 75% (95% CI, 61%–85%), with 13% CR and 62% PR with median DoR and PFS not reached at the time. In a long-term follow-up analysis, out of 153 patients, 121 patients (79%; 95% CI, 72–85) had objective response with 16% having a CR, 63% having a PR, and 12% having stable disease. The median DoR was 35.2 months (22.8–NE) and the median PFS was 28.3 months.[26] Both larotrectinib and entrectinib are FDA-approved for *NTRK* gene fusion solid tumors for patients who have progressed following treatment or have no satisfactory standard therapy.[27,28]

Results from a recent pivotal phase 1/2 TRIDENT-1 trial presented at ESMO Congress, 2023[29] showed robust responses and durable clinical activity of repotrectinib, a next-generation ROS1 and TRK tyrosine kinase inhibitor (TKI) in both TKI-naïve and -pretreated patients with *NTRK* fusion-positive (*NTRK*+) solid tumors, including non-small cell lung cancer (NSCLC). In a multicenter, single-arm, open-label, multi-cohort trial, efficacy was evaluated in 48 patients with locally advanced or metastatic *NTRK* gene fusion-positive solid tumors who had received a prior TRK TKI and 40 patients who were TKI naïve. Confirmed ORR in the TKI-naïve group was 58% (95% CI: 41-73) and 50% (95% CI: 35-65) in the TKI-pretreated group. Median DoR was NE (95% CI: NE-NE) in the TKI-naïve group and 9.9 months (95% CI: 7.4-13.0) in the TKI-pretreated group. Based on these trial data, the FDA granted accelerated approval to repotrectinib for patients with locally advanced or metastatic solid tumors that have an *NTRK* gene fusion, and that have progressed following treatment or have no satisfactory alternative therapy.[30] The NCCN Panel added the repotrectinib regimen for *NTRK* gene fusion-positive tumors under useful in certain circumstances for second-line or subsequent therapy.

HER2

HER2 expression is observed in a wide range of solid tumors and is an established prognostic biomarker for breast, gastric, and colorectal cancers. Cervical cancer has shown a HER2 positivity rate of approximately 2% to 6% in the literature.[31-33] Trastuzumab deruxtecan is an antibody-drug conjugate that contains the humanized anti-HER2 monoclonal antibody trastuzumab attached to the topoisomerase inhibitor deruxtecan.[34] Another tumor-agnostic study evaluated the durability and clinically meaningful response of trastuzumab deruxtecan across multiple HER2-expressing (IHC 3+ or 2+) advanced solid tumor types in patients who progressed on prior therapy or who have no satisfactory alternative treatment options.

The DESTINY-PanTumor02 is an open-label, multicenter, phase 2 trial that evaluated trastuzumab deruxtecan in 267 patients with HER2-expressing (IHC 3+ or 2+) locally advanced or metastatic disease after ≥1 systemic treatment or without alternative treatments. The study included 40 patients with cervical cancer with IHC2+ or 3+ expression of HER2. Overall, the ORR was 37.1% (n = 99; [95% CI, 31.3–43.2]), the median PFS was 6.9 months (95% CI, 5.6–8.0), and the median OS was 13.4 months (95% CI, 11.9–15.5). In patients with cervical cancer, the confirmed ORR was 50% and for the HER2 IHC3+ cohort, the ORR was 75% and the median OS was 13.6 months.[35] The Panel recommends HER2 IHC testing (with or without reflex to HER2 FISH for equivocal IHC) for advanced, metastatic, or recurrent vaginal cancer. The Guidelines

include fam-trastuzumab deruxtecan-nxki as category 2A, useful in certain circumstances, second-line/subsequent therapy option for HER2-positive tumors (IHC 3+ or 2+).

RET Gene Fusion

RET gene fusions most commonly occur in thyroid and NSCLCs and are observed in <1% of patients with other solid tumors. The prognosis of disease in this small subset of patients who have progressed on or following prior systemic therapy is poor. The phase 1–2, multicenter, open-label trial, Libretto-001, evaluated the efficacy of selpercatinib in patients with *RET*-mutant advanced solid tumors. In an interim analysis of the trial in a tumor-agnostic population, the efficacy and safety of selpercatinib was investigated in 41 patients with *RET* fusion-positive solid tumors (other than NSCLC and thyroid cancer) with disease progression on or after previous systemic therapies or who had no satisfactory therapeutic options. The ORR was 44% (95% CI, 28.5–60.3), with a median DoR of 24.5 months (95% CI, 9.2–NE).[36,37] Selpercatinib received tumor-agnostic approval by the FDA for patients with solid tumors with a *RET* gene fusion that has progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. Comprehensive molecular profiling can be considered by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory including at least microsatellite instability (MSI), TMB testing, *NTRK*, and *RET* for predicting rare pan-tumor targeted therapy. The NCCN Panel also recommends selpercatinib as a biomarker-directed second-line/subsequent therapy under useful in certain circumstances category for vaginal cancer.

HPV Status/p16

High p16 expression was associated with long-term survival in individuals AFAB with primary carcinoma of the vagina, but the only independent predictors for survival were tumor size and histopathologic grade. The p16 and Ki-67 expression might be useful in tumor grading, and p16 expression can be used as a marker for HPV positivity.[38] The p16 marker has a significant prognostic value in vaginal cancers across all tumor stages. In a retrospective chart review from 1997 to 2006,[39] 43 patients with vaginal cancer were evaluated by IHC staining for the presence of p16 and Ki-67 markers, and survival data were examined.

Patients with vaginal cancer (n = 31) with a p16 positive diffuse staining had significantly improved survival (~49.5 months; *P* = .003) compared with patients with p16-negative disease (~25.3 months). Stage-specific analysis showed a significant survival benefit for p16-positive vaginal cancers compared with p16-negative cancers for stages I and II (*P* = .017; hazard ratio [HR], 0.400; 95% CI, 0.189–0.850) and stages III and IV (*P* = .001; HR, 0.176; 95% CI, 0.066–0.479).[39] There are several systematic reviews emphasizing the positive prognostic value of HPV and p16 positivity in vaginal cancer.[40,41] The NCCN Panel recommends ancillary testing to determine HPV status either by p16 IHC or RNA in situ hybridization (ISH) or by DNA sequencing.

p53 IHC

p53 mutations are common in HPV-negative malignancies in older women, and they are linked to an increased risk of mortality.[7] In vulvar cancer, p16 and p53 IHC have established prognostic value, stratifying patients into three groups based on the HPV and *TP53* mutation status of the tumor. p53 positivity is associated with poor prognosis and significantly increased recurrence and disease-specific mortality in gynecologic cancers.[42] The *TP53* mutations are present in typical keratinizing carcinomas and precursor lesions with elevated risk for gynecologic cancers. *TP53* mutation seems to occur early in vulvar carcinogenesis and is a useful marker, especially in lesions with increased risk of carcinoma.[43] While HPV types 16 and 18 might play a common causal role in cervical carcinoma, p53 gene mutations might be

a main causal factor for carcinogenesis in vulvar carcinoma. Vaginal carcinoma is considered to have transitional characteristics between cervical and vulvar carcinoma.[44] p53 testing by IHC is recommended in HPV-negative cancers. NGS is an acceptable alternative for p53 testing.

Primary Treatment

Most of the trial data cited within this section are primarily for cervical cancer that has been generalized to vaginal cancer.

Invasive (Stage I–IVA) Disease

The primary treatment for early-stage vaginal cancer is radiation therapy (RT) and surgical resection. For the majority of vaginal cancers, radiation is used rather than surgery as primary treatment due to improved organ preservation. For invasive stage I cancer, RT is the preferred regimen with only intracavitary brachytherapy in select favorable patients with small lesions <2 cm and limited thickness (≤5 mm). For >2 cm lesions confined to the vagina, external beam RT (EBRT) with intracavitary brachytherapy or interstitial brachytherapy if >0.5 cm residual thickness at brachytherapy with/without concurrent platinum-containing chemotherapy is recommended.

Another option for patients with invasive stage I disease is surgical resection with or without lymph node assessment only for select patients. Surgery is only recommended if a complete resection with clear margins is feasible without excessive morbidity and with the likelihood that no adjuvant RT would be required. Pelvic lymph nodes need to be assessed for proximal lesions involving the upper two thirds of the vagina, while inguinal lymph nodes should be assessed for distal lesions involving the lower one-third of the vagina. Surgery is only recommended if a complete resection with clear margins is feasible without excessive morbidity and with likelihood that no adjuvant RT would be required. Vaginectomy may be considered for small lesions for which margins are likely to be negative.

For microscopic lesions at the top of the vagina, upper vaginectomy ± hysterectomy may be reasonable. A radical hysterectomy may be appropriate for macroscopic lesions (<2 cm). Every effort should be made to obtain negative margins. With postoperative risk factor of close or positive margin(s) for invasive disease or positive lymph nodes, adjuvant RT or chemoradiation and/or brachytherapy is recommended. The management of positive margins for HSIL should be individualized.

For invasive stage II–IVA disease, the preferred modality for definitive management is platinum-based chemoradiation with brachytherapy. Concurrent chemotherapy has been shown in many series to improve outcomes and is often used in stage II–IV disease. Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant). EBRT with brachytherapy is also a recommended regimen for patients with stage II–IVA disease. The addition of brachytherapy to EBRt is preferred as the combination has been shown to improve disease control.

For more information on the important phase 3 clinical trials underpinning treatment recommendations for cervical cancer that were adapted for vaginal cancer, see the NCCN Clinical Guidelines for Cervical Cancer.

Surveillance

The Panel agrees with the new Society of Gynecologic Oncology (SGO) recommendations for post-treatment surveillance.[45] The recommended surveillance is based on the patient's risk for recurrence and personal preferences. History and physical examinations are recommended every 3 to 6 months for 2 years, every 6 to 12 months for another 3 to 5 years, and then annually.

Many of the recommendations for staging and follow-up of primary vaginal cancer are derived from cervical cancer and they have generalizability to vaginal cancer due to similar tumor biology. The radiation guidance and

recommendations for cervical cancer can be extrapolated to vaginal cancer and the principles of post-chemoradiation tumor response evaluation are largely analogous.[46] Early post-treatment imaging is generally performed following a period of approximately 3 to 4 months after the completion of chemoradiation to assess response.[46] Further imaging is needed as indicated based on symptoms or examination findings suspicious for recurrence. However, recurrence should be proven by biopsy before proceeding with treatment planning.

Annual cervical/vaginal cytology tests can be considered as indicated for detection of lower genital tract dysplasia (eg, for those who have had fertility-sparing surgery), which includes HPV testing. Some clinicians have suggested that rigorous cytology follow-up is not warranted because of studies stating that Pap cytology did not detect recurrences in patients with stage I or II cervical cancer who were asymptomatic after treatment.[45,47,48] Noting the inherent differences between these patients and the general screening population, the Panel does not recommend workup of low-grade squamous dysplasia detected during surveillance, but suggests that patients should follow up with a provider with specific expertise in this area. It is important to emphasize good clinical evaluation and a high index of suspicion, because the detection rate of recurrent genital tract cancer is low using cervical and vaginal cytology alone.[49]

Many other tests remain optional based on clinical indications, such as semiannual CBCs, blood urea nitrogen (BUN), and serum creatinine determinations. Patients with persistent or recurrent disease need to be evaluated using additional imaging studies as clinically indicated, biopsy with or without EUA, and surgical exploration in selected cases followed by therapy for relapse (see *Therapy for Relapse*).[50] Comprehensive molecular profiling as determined by FDA-approved assay or a validated test performed in a CLIA-certified laboratory can be considered for better selection of systemic therapy. If tissue biopsy of a metastatic site is not feasible or tissue is not available, comprehensive genomic profiling via a validated plasma circulating tumor DNA (ctDNA) assay can be considered.

Education of patients regarding symptoms suggestive of recurrence is recommended (eg, vaginal discharge; weight loss; anorexia; pain in the pelvis, hips, back, or legs; persistent coughing). Patients should also be counseled on healthy lifestyle, obesity, nutrition, exercise, sexual health (including vaginal dilator use and lubricants/moisturizers), hormone replacement therapy (local estrogen and hormone therapy for menopause), and potential long-term and late effects of treatment. Smoking cessation and abstinence should be encouraged.[45] See the NCCN Guidelines for Survivorship, the NCCN Guidelines for Smoking Cessation, and https://www.cancer.org/cancer/survivorship.

Cervical cancer survivors are at risk for second cancers such as vaginal cancer.[51] Data suggest that patients who undergo RT for pelvic cancers are at risk for radiation-induced second cancers, especially at radiated sites near the cervix (eg, colon, rectum/anus, urinary bladder); therefore, careful surveillance is appropriate for these patients.[52,53]

Therapy for Relapse

Recurrences should be proven by biopsy before proceeding to treatment planning for recurrent disease.

Locoregional Recurrence

For patients who experience locoregional recurrences who have not undergone previous RT or who experience recurrences outside of the previously treated RT field, therapy for relapse includes tumor-directed EBRT and/or brachytherapy or EBRT with concurrent platinum-containing chemotherapy and/or brachytherapy. Typically, the chemoradiation for recurrence uses cisplatin as a single agent or carboplatin (if cisplatin intolerant).[54,55] However, in those patients who have relapsed soon after

completing initial chemoradiation with these regimens, other systemic therapy options might be considered or best supportive care could be offered (see NCCN Guidelines for Palliative Care).

For patients with locoregional recurrences with prior intracavitary brachytherapy only, individualized EBRT with/without systemic therapy and/or interstitial brachytherapy is recommended. Concurrent surgery is only recommended if a complete resection with clear margins is feasible without excessive morbidity.

Patients with central pelvic recurrent disease after prior EBRT and/or brachytherapy should be evaluated for pelvic exenteration with (or without) intraoperative RT (IORT), although IORT is category 3 for both cervical and vaginal cancers.[56-63] Surgical mortality is generally ≤5%, with survival rates approaching 50% in carefully selected patients.[59] Concomitant measures with these radical procedures include adequate rehabilitation programs dealing with the psychosocial and psychosexual consequences of the surgery as well as reconstructive procedures.[58,64-66] In carefully selected patients, reirradiation or local excision is also recommended. See *Principles of Radiation Therapy* for more information.

For patients with noncentral recurrent disease, options include systemic therapy or resection with (or without) IORT (category 3 for IORT), reirradiation or best supportive care (see NCCN Guidelines for Palliative Care), or participation in a clinical trial.

Patients who experience recurrence after second-line definitive therapy, either surgery or RT, have a poor prognosis. They can be treated with systemic therapy or best supportive care or can be enrolled in a clinical trial.

Stage IVB or Recurrent Distant Metastatic Disease

Limited Disease

For stage IVB patients or patients with recurrent metastases with limited disease, systemic therapy is one of the options. Comprehensive molecular profiling as determined by FDA-approved assay, or a validated test performed in a CLIA-certified laboratory can be considered for better selection of systemic therapy. Local treatment of the primary disease by chemoradiation with/without brachytherapy can be considered. Local treatment of metastases can also be considered that includes surgery for select patients or individualized EBRT or other local ablative therapies such as radiofrequency ablation, cryoablation, or stereotactic body RT (SBRT).

Disseminated Disease

Patients who develop distant metastases, either at initial presentation or at relapse, are rarely curable. Comprehensive molecular profiling as determined by FDA-approved assay can be considered for better selection of systemic therapy. For patients with disseminated disease, systemic therapy with/without palliative RT and best supportive care are recommended. Patients who may benefit from aggressive local therapy for oligometastatic disease include those with nodal, lung, liver, or bone metastases.[67,68]

The palliation of pelvic recurrences in heavily irradiated sites that are not amenable to local pain control techniques or to surgical resection is difficult.[69] These sites are generally not responsive to chemotherapy. Adequately palliating the complications of pain and fistulae from these recurrences is clinically challenging (https://emedicine.medscape.com/article/270646-overview). However, short courses of RT may provide symptomatic relief to patients with bone metastases, painful para-aortic nodes, or supraclavicular adenopathy.[70-72] For most other patients with distant metastases, an appropriate approach

is a clinical trial, chemotherapy, or best supportive care (see NCCN Guidelines for Palliative Care).

Systemic Therapy Recommendations

The data cited within this section are primarily for cervical cancer and have been generalized to vaginal cancer. Because of the uncommon nature of vaginal cancer and its similarities to cervical cancer, many of the treatment options are derived from those for cervical cancer. The systemic therapy recommendations for primary vaginal cancer are extrapolated from cervical cancer since they share similar disease etiologies. There are no category 1 treatment recommendations for vaginal cancer due to lack of disease site-specific phase 3 trial data. The majority of cases in the vagina might be arising from another site and the treatment recommendations will be based on corresponding NCCN treatment Guidelines.

Chemoradiation for Locally Advanced Vaginal Cancer

Concurrent chemoradiation, using platinum-containing chemotherapy (cisplatin alone [preferred]), is the treatment of choice for stages IB3, II, III, and IVA disease based on results from randomized clinical trials. These trials have shown that the use of concurrent chemoradiation results in a 30% to 50% decrease in the risk of death compared with RT alone. Long-term follow-up of three trials has confirmed that concurrent cisplatin-containing chemoradiation improves PFS and OS when compared with RT with (or without) hydroxyurea.[73-75] Cisplatin remains the preferred radiosensitizing agent in the primary treatment for patients with locally advanced cervical cancer when used concomitantly with EBRT and carboplatin is a preferred radiosensitizing agent for patients who are cisplatin intolerant.[76] When cisplatin and carboplatin are unavailable, the other recommended options are capecitabine/mitomycin IV, gemcitabine, and paclitaxel as radiosensitizers based on a few early-phase studies that have shown their efficacy and tolerability when administered concomitantly with radiation.[77-79] A phase 3, randomized trial enrolling 926 patients with locally advanced, stage IIB–IVA cervical cancer evaluated the efficacy of RT plus concurrent chemotherapy consisting of oral 5-fluorouracil (5-FU)/mitomycin as compared to RT only, RT plus adjuvant chemotherapy (5-FU), or RT plus concurrent chemoradiotherapy plus adjuvant chemotherapy.[77] Although acute side effects were more prevalent in the concurrent arms and the OS was not significant between the arms, the RT plus concurrent chemotherapy arm showed the least locoregional recurrence and the highest 5-year disease-free survival (DFS) when compared with the other arms. In particular, the difference in DFS and OS rate was highly significant when comparing the concurrent chemoradiation arm with the RT-only arm (P = .0001). Several studies have shown that although 5-FU/mitomycin combined with RT was effective, the combination is also associated with relatively higher toxicity rates and should be used with caution.[80,81] The efficacy and safety of gemcitabine combined with pelvic radiation was tested in 19 patients with chemo-naïve, advanced-stage IIIB cervical cancer and showed a CR of 89.5% and PR of 5.3% for an ORR of 94.7%. The OS at median follow-up time of 19.9 months was 100% with DFS of 84.2%. Due to gemcitabine's high potency as a radiosensitizer, it requires reduced dosing when used concurrently with radiation to avoid radiation toxicity.[78] In a comparative study, the disease control and toxicity profile were found to be similar between cisplatin and gemcitabine.[82] The benefit of paclitaxel alone as a radiosensitizer has not been extensively studied in the literature and there are only a few known preclinical or early-phase studies of its efficacy. In a pilot study to evaluate paclitaxel with RT, CR was achieved by 8 out of 13 patients with locally advanced cervical cancer and by 4 out of 6 patients treated with a recurrent disease.[83] Although chemoradiation is tolerated, acute and long-term side effects have been reported.[84-86] Due to significant toxicity concerns associated with these agents, cisplatin or carboplatin is a preferred agent over other non-platinum chemoradiation regimens.

The NCCN Panel has noted for all chemoradiation agents that the cost and toxicity profiles of these radiosensitizing agents should be considered when selecting an appropriate regimen for treatment and have strongly expressed that this is especially critical when these regimens are being used for extended-field RT where toxicities may be more severe.

Systemic Therapy for Recurrent or Metastatic Vaginal Cancer

Systemic therapy with or without radiation forms the basis of treatment of patients with recurrent or metastatic disease.

First-Line Systemic Therapy Options

Preferred Regimens

Pembrolizumab Plus Chemotherapy With or Without Bevacizumab as First-Line Therapy

The NCCN Guidelines for Cervical Cancer include two immunotherapy-based regimens as preferred, first-line therapy options for the treatment of PD-L1–positive recurrent or metastatic cancer, and that recommendation is extrapolated to vaginal cancer management as well. Pembrolizumab combined with chemotherapy with or without bevacizumab regimens is a preferred treatment option based on the results of the KEYNOTE-826 study.[15] In the primary analysis of the phase 3, KEYNOTE-826 trial, which enrolled 617 patients (548 with PD-L1–positive CPS ≥1 tumors; 317 patients with CPS ≥10) with previously untreated persistent, recurrent, or metastatic cervical cancer, the addition of pembrolizumab to chemotherapy with or without bevacizumab improved PFS and OS versus the placebo group (PFS, 10.4 vs. 8.2 months, respectively; HR, 0.65; 95% CI, 0.53–0.79; $P < .001$, and OS at 24 months: 50.4% vs. 40.4%, respectively; HR, 0.67; 95% CI, 0.54–0.84; $P < .001$). The ORR was significantly higher in the pembrolizumab arm as compared to the placebo group in patients with PD-L1–positive (CPS ≥1) tumors (68.1% vs. 50.2%). The FDA approved pembrolizumab plus chemotherapy, with or without bevacizumab for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1). In the final updated analysis of the trial results, the addition of pembrolizumab to chemotherapy with or without bevacizumab continued to show significant survival benefits in the PD-L1–positive (CPS ≥1) tumors at a median follow-up of 39.1 months with a median OS and PFS of 28.6 and 10.5 months versus 16.5 and 8.2 months in the pembrolizumab plus chemotherapy arm versus the placebo plus chemotherapy arm, respectively (HR, 0.60; 95% CI, 0.49–0.74; $P < .0001$).[87]

Platinum-based chemotherapy (cisplatin or carboplatin)/paclitaxel with bevacizumab has been extensively investigated in clinical studies and is listed in the NCCN Guidelines as a preferred, first-line treatment option for patients with recurrent/metastatic vaginal cancer (based on the GOG 240 trial).

A randomized phase 3 trial (GOG 240) studied the addition of bevacizumab to combination chemotherapy regimens (cisplatin/paclitaxel/bevacizumab or topotecan/paclitaxel/bevacizumab) in 452 patients in the first-line setting of metastatic, persistent, or recurrent cervical cancer. Analysis of pooled data from the two chemotherapy regimens revealed significant improvements in OS among patients receiving bevacizumab (16.8 vs. 13.3 months; $P = .007$).[88] While bevacizumab led to higher toxicity (eg, hypertension, thromboembolic events, gastrointestinal [GI] fistula), it was not associated with a statistically significant decrease in patient-reported quality of life ($P = .27$).[89] A 2017 systemic review and meta-analysis of data from 19 trials of systemic therapy for patients with recurrent, persistent, or metastatic cervical cancer found a trend towards improved OS for the addition of bevacizumab to cisplatin/paclitaxel or topotecan/paclitaxel when compared with all other non-bevacizumab–containing chemotherapy regimens.[90]

The published data from a phase 3 randomized trial (JCOG0505) suggested that carboplatin/paclitaxel was non-inferior to cisplatin/paclitaxel in 253 patients with metastatic or recurrent cervical cancer.[91] Many physicians use carboplatin/paclitaxel because of ease of administration and tolerability.[92] Results from JCOG0505 showed that the paclitaxel/carboplatin regimen was non-inferior to paclitaxel/cisplatin in terms of median OS (18.3 months for paclitaxel/cisplatin vs. 17.5 months for paclitaxel/carboplatin; HR, 0.994 [90% CI, 0.79–1.25]; *P* = .032) and non-hospitalization periods were significantly longer for patients receiving paclitaxel/carboplatin.[91] However, among patients who had not received prior cisplatin, OS for carboplatin/paclitaxel and cisplatin/pacltaxel was 13.0 and 23.2 months, respectively (HR, 1.571; 95% CI, 1.06–2.32).[91] Based on these data, the Panel recommends carboplatin/paclitaxel as a preferred option for patients who have received prior cisplatin therapy.

A systematic review of the data on cisplatin/paclitaxel and carboplatin/paclitaxel regimens also suggested that lower toxicity carboplatin-based regimens appear to be an equally effective alternative to cisplatin-containing regimens for treating recurrent or metastatic cervical cancer.[93] Based on the collective findings from GOG 240 and JGOG0505, the Panel has included carboplatin/paclitaxel/bevacizumab as an additional preferred regimen for recurrent or metastatic vaginal cancer.

Other Recommended Regimens

Cisplatin is generally regarded as the most active agent and is recommended as a first-line single-agent chemotherapy option for recurrent or metastatic vaginal cancer; reported response rates for cervical cancer are approximately 20% to 30%, with an occasional CR.[94-97] OS with cisplatin is approximately 6 to 9 months. Both carboplatin and paclitaxel have each been reported to be tolerable and efficacious and are also possible first-line single-agent chemotherapy options.[98-102] Therefore, palliation with single agents—cisplatin, carboplatin, or paclitaxel—is a reasonable approach in patients with recurrent disease not amenable to surgical or radiotherapeutic approaches. However, most patients who develop metastatic disease have received concurrent cisplatin/RT as primary treatment and may no longer be sensitive to single-agent platinum therapy.[97,103]

Cisplatin/paclitaxel, carboplatin/paclitaxel, topotecan/paclitaxel/bevacizumab, topotecan/paclitaxel, and cisplatin/topotecan are also recommended as appropriate alternate options under the other recommended regimens category.[88,97,103-106] A randomized phase 3 study (GOG 169) in 264 patients compared cisplatin/paclitaxel versus cisplatin alone for metastatic, recurrent, or persistent cervical cancer. Patients receiving the 2-drug combination had a higher response rate (36% vs. 19%) and improved PFS (4.8 vs. 2.8 months; *P* > .001) compared to single-agent cisplatin, although no improvement was seen in median survival.[97] Patients whose disease responded to cisplatin/paclitaxel had a significant improvement in quality of life. Another randomized phase 3 study (GOG 179) in 294 patients investigated cisplatin/topotecan versus cisplatin alone for recurrent or persistent cervical cancer. The topotecan combination regimen was shown to be superior to single-agent cisplatin with respect to ORR (27% vs. 13%; *P* = .004), PFS (4.6 vs. 2.9 months; *P* = .014), and median survival (9.4 vs. 6.5 months; *P* = .017).[103] The FDA has approved cisplatin/topotecan for advanced cervical cancer. However, the cisplatin/paclitaxel or carboplatin/paclitaxel regimens are less toxic and easier to administer than cisplatin/topotecan.[107]

A phase 3 trial (GOG 204) compared four cisplatin-doublet regimens (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/vinorelbine) in 513 patients with advanced metastatic or recurrent cervical cancer.[106] The trial was closed early based on futility analysis, because it was apparent that the cisplatin/topotecan,

cisplatin/gemcitabine, and cisplatin/vinorelbine regimens were not superior to the control arm of cisplatin/paclitaxel. No significant differences in OS were seen; however, the trends for response rate, PFS, and OS (12.9 vs. 10 months) suggest that cisplatin/paclitaxel is superior to the other regimens. Cisplatin/paclitaxel was associated with less thrombocytopenia and anemia (but with more nausea, vomiting, infection, and alopecia) than the other regimens. While topotecan/paclitaxel was not shown to be superior to cisplatin/paclitaxel, it may be considered as an alternative in patients who are not candidates for cisplatin.[88]

Based on previous studies, cisplatin/paclitaxel and carboplatin/paclitaxel have become the most widely used systemic regimens for metastatic or recurrent cervical cancer and this is also recommended for vaginal cancer. However, for patients who may not be candidates for taxanes, cisplatin/topotecan remains a reasonable alternative regimen.[103]

Second-Line/Subsequent Systemic Therapy Options

Immunotherapy as Preferred, Second-Line/Subsequent Therapy

Increasingly available data from several prospective studies have demonstrated the effectiveness of immunotherapies or specific biomarker-based therapies in the setting of disease progression and have significantly transformed the management of cervical cancer. In addition, many biomarker-specific therapies have demonstrated meaningful clinical efficacy and durability regardless of the underlying tumor type leading to an increase in tumor-agnostic regulatory approvals.

Pembrolizumab as a Preferred, Second-Line/Subsequent Therapy

Pembrolizumab is an FDA-approved therapy for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy for PD-L1–positive tumors (CPS ≥1). It is also approved for unresectable or metastatic MSI-H/dMMR or TMB-H solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. In the NCCN Guidelines, pembrolizumab monotherapy is the preferred, second-line therapy option for recurrent/metastatic MSI-H/dMMR or TMB-H or PD-L1–positive tumors based on the results from KEYNOTE-028 (phase 1b) and KEYNOTE-158 (phase 2) trials.[22,108,109]

Chemotherapy as Other Recommended, Second-Line/Subsequent Therapy

Other recommended agents that have shown responses or prolongation of PFS and may be useful as second-line therapy include bevacizumab,[106] albumin-bound paclitaxel (ie, nab-paclitaxel),[110] docetaxel,[111] fluorouracil,[112] gemcitabine,[113] ifosfamide,[114,115] irinotecan,[116] mitomycin,[117] pemetrexed,[118] topotecan,[119,120] and vinorelbine.[121]

Tisotumab vedotin-tftv (TV) is also recommended for second-line or subsequent therapy for recurrent or metastatic vaginal cancer based on the innovaTV-204 trial. This phase 2 single-arm study evaluated the efficacy of TV in 102 patients with recurrent or metastatic cervical cancer who had progressed on previous systemic therapy.[122] At the median follow-up of 10 months, the confirmed ORR was 24% (95% CI, 16–33), which included a 7% CR and 17% PR, and the median DoR was 8.3 months (95% CI, 4.2–NR). Following the results from the innovaTV-201 and innovaTV-204 trials that showed clinically meaningful and durable activity of TV against pretreated recurrent/metastatic cervical cancer, the FDA granted accelerated approval for adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.[123] The results from the phase 3, randomized, innovaTV-301/ENGOT-cx12/GOG-3057 trial were recently published at ESMO Congress 2023.[124] Among the 502 patients who were randomized (TV: 253; chemotherapy: 249); the TV arm had a 30% reduction in risk of death versus chemotherapy (HR, 0.70; 95% CI, 0.54–0.89; P = .0038). The results showed a median follow-up of 10.8 months (95% CI, 10.3–11.6), with significantly longer median OS (11.5 months [95% CI, 9.8–

14.9] versus 9.5 months [95% CI, 7.9–10.7]). PFS was superior in the TV versus chemotherapy arm (HR, 0.67; 95% CI, 0.54–0.82; *P* < .0001). Confirmed ORR was 17.8% and 5.2% in the TV and chemotherapy arms, respectively (odds ratio [OR], 4.0; 95% CI, 2.1–7.6; *P* < .0001).

Cemiplimab is a PD-1–blocking monoclonal activity shown to have anti-tumor activity against cervical cancer. The phase 3, randomized, Empower-Cervical-1 clinical trial evaluated the efficacy of cemiplimab or investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) in patients with recurrent or metastatic cervical cancer who have progressed on prior therapy.[125] The trial enrolled 608 patients, who had previously received one or more lines of systemic therapy for recurrence, and 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 achieved an OR (95% CI, 12.5–21.1) as compared to 6.3% (95% CI, 3.8–9.6) in the chemotherapy arm. The median OS in SCC and adenocarcinoma/adenosquamous carcinoma of the cervix in the cemiplimab versus chemotherapy arm was 11.1 versus 8.8 months (HR, 0.73; 95% CI, 0.58–0.91) and 13.3 versus 7 months (HR, 0.56; 95% CI, 0.36–0.85), respectively, indicating that there is an OS benefit irrespective of histology. In a sub-analysis of the study, samples from 254 patients were evaluated for PD-L1 expression to test the efficacy of cemiplimab in tumors with PD-L1 expression of ≥1%. The median OS of cemiplimab-treated PD-L1–expressed tumors (CPS ≥1) versus chemotherapy was 13.9 versus 9.3 months (HR, 0.70; 95% CI, 0.46–1.05) while the OS benefit for tumors with low PD-L1 expression (CPS <1) was comparable in the two arms, although the study authors noted that due to smaller size of the sub-group population, reliable assessment of the benefits could not be made. According to the patient-reported outcomes,[126] cemiplimab conferred favorable differences in global health status (GHS)/quality of life and physical functioning compared with chemotherapy among patients with recurrent cervical cancer, and clinically meaningful differences favoring cemiplimab in role functioning, appetite loss, and pain. In the recent version of the NCCN Guidelines for Vaginal Cancer, cemiplimab was moved to other recommended regimens as a second-line/subsequent-therapy option.

Biomarker-Directed, Useful in Certain Circumstances, Second-Line/Subsequent Therapy

The NCCN Guidelines for Vaginal Cancer have included a list of biomarkers with their associated targeted treatments as second-line/subsequent therapies under "useful in certain circumstances" options. The *Principles of Pathology* section of the Guidelines provides recommendations for individual biomarkers that should be evaluated for targeted therapy.

Nivolumab for PD-L1–Positive Tumor

Nivolumab, a checkpoint inhibitor, has shown efficacy in patients with recurrent/metastatic cervical cancer who received at least one prior chemotherapy regimen. Based on Checkmate-358 data (see *Prognostic and Predictive Biomarkers* section), this recommendation is part of the 1.2025 version of NCCN Guidelines for Vaginal Cancer.

Trastuzumab Deruxtecan for HER2-Positive Tumor

Another tumor-agnostic study evaluated the durability and clinically meaningful response of trastuzumab deruxtecan across multiple HER2-expressing (IHC 3+ or 2+) advanced solid tumor types in patients who progressed on prior therapy or who have no satisfactory alternative treatment options. HER2 expression is observed in a wide range of solid tumors and is an established prognostic biomarker for breast, gastric, and colorectal cancers. Cervical cancer has shown a HER2 positivity rate of approximately 2% to 6% in the literature.[31-33] Trastuzumab deruxtecan is an antibody-drug conjugate that contains the humanized anti-HER2

monoclonal antibody trastuzumab attached to the topoisomerase inhibitor deruxtecan.[34]

Based on the DESTINY-PanTumor02 trial (see *Prognostic and Predictive Biomarkers* section), Version 1.2025 of the NCCN Guidelines for Vaginal Cancer includes fam-trastuzumab deruxtecan-nxki as a category 2A, useful in certain circumstances, second-line/subsequent therapy option for HER2-positive tumors (IHC 3+ or 2+). The Panel recommends HER2 IHC testing (with reflex to HER2 FISH for equivocal IHC) for vaginal cancer.

Selpercatinib for RET Gene Fusion Tumor
Selpercatinib received tumor-agnostic approval by the FDA for patients with solid tumors with a *RET* gene fusion that has progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. The NCCN Panel recommends selpercatinib as a biomarker-directed second-line/subsequent therapy under useful in certain circumstances category for *RET* gene fusion-positive tumors given its efficacy in tumor-agnostic population. The NCCN Panel also specified that *RET* gene fusion testing may be considered for patients with vaginal cancer (see *Prognostic and Predictive Biomarkers* section).

TRK Inhibitors for NTRK Gene Fusion Tumor
In addition to selpercatinib, other targeted therapy regimens included in the NCCN Guidelines for Vaginal Cancer as biomarker-directed second-line/subsequent therapies that have been approved in a tumor-agnostic population are the TRK inhibitors, larotrectinib and entrectinib. Larotrectinib targets the TRK proteins that are encoded by the genes *NTRK1*, *NTRK2*, and *NTRK3*. *NTRK* gene fusions are found in about 1% of all solid tumors. The NCCN Guidelines for Vaginal Cancer recommend larotrectinib, entrectinib, and repotrectinib as a second-line or subsequent, useful in certain circumstances option for *NTRK* gene fusion-positive tumors based on FDA approval and several clinical trials (see *Prognostic and Predictive Biomarkers* section).

Principles of Radiation Therapy

RT is preferred in the management of vaginal cancer rather than surgery as primary treatment due to improved organ preservation. Preferred modalities for definitive management include either concurrent pelvic chemoradiation (platinum-based) and brachytherapy or EBRT and brachytherapy. The addition of brachytherapy to external beam is preferred as the combination has been shown to improve control. The overall treatment time should not extend beyond 8 weeks and treatment delays and interruptions need to be minimized.

The algorithm provides general RT dosage recommendations, which should not be interpreted as stand-alone recommendations because RT techniques and clinical judgment are an essential part of developing an appropriate treatment regimen.

Since vaginal cancer is rare, prospective trials of patients with vaginal cancer have not been feasible, and single-institutional reports of clinical outcomes spanning several decades have been the evidence for current treatment recommendations. The management of vaginal cancer is currently extrapolated from prospective studies of cervical cancer, due to their similarities in disease etiology.[127] The radiation guidance and recommendations for cervical cancer can be extrapolated to vaginal cancer and the principles of post-chemoradiation tumor response evaluation are largely analogous.[46]

Radiation Treatment Planning

Technologic advances in imaging, computer treatment planning systems, and linear accelerator technology have enabled the more precise delivery of radiation doses to the pelvis. However, physical accuracy of dose delivery must be matched to a clear understanding of tumor extent, potential pathways of spread, and historical patterns of locoregional recurrence to avoid geographic misses.

Pelvic MRI with and without IV contrast and vaginal gel to assess local disease extent is the preferred workup. The neck/chest/abdomen/pelvis/groin FDG-PET/CT is preferred to evaluate metastatic disease. The chest/abdomen/pelvis CT is also recommended. Other initial imaging should be based on symptomatology and clinical concern for metastatic disease.

CT-based treatment planning with conformal blocking and dosimetry is considered standard care for EBRT. As with cervical cancer, FIGO encourages the use of advanced imaging modalities (CT, MRI, and PET) to guide therapy, although in under-resourced settings the imaging findings may not be used to determine the stage to preserve the FIGO system.

In patients who are not surgically staged, FDG-PET imaging is useful to help define the nodal volume of coverage and may be useful postoperatively to confirm removal of abnormal nodes.[128] FDG–PET/CT imaging is preferred at 3 to 4 months after RT. MRI is also needed if FDG-PET/CT is difficult to obtain or needed for clarification or exam findings. Repeating imaging is also recommended if clinically indicated. IMRT technique is preferred to minimize toxicities in definitive treatment of the pelvis with or without para-aortic treatment. Adaptive planning with image-guided RT (IGRT), especially if IMRT is utilized, is encouraged. Brachytherapy is an important component of definitive therapy in patients with vaginal cancer, although brachytherapy alone is not recommended for most tumors, even early-stage, due to a high recurrence rate.[129] Brachytherapy is typically combined with EBRT in an integrated treatment plan. SBRT allows delivery of very high doses of focused EBRT and may be applied to isolated metastatic sites.[130,131] Local ablative therapies such as SBRT are recommended for patients with stage IVB disease or patients with recurrent distant metastases, with limited disease.

Concepts regarding the gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), organs at risk (OARs), and dose-volume histogram (DVH) have been defined for use in image-guided adaptive brachytherapy (IGABT).[132,133]

There are increasing efforts to use and standardize image-based volumetric brachytherapy approaches using MRI, CT, or ultrasound. International validation efforts with different studies including the EMBRACE-I study, which is a benchmark study that represents a positive breakthrough in the treatment of locally advanced cervical cancer, are underway.[134-140]

Brachytherapy

Brachytherapy is encouraged for all suitable patients with primary vaginal cancer. Orton et al[141] evaluated the impact of brachytherapy on survival in patients with vaginal cancer who received radiotherapy. Based on the two retrospective cohorts (women who received EBRT alone and those who received brachytherapy [alone or in combination of EBRT]), median OS for patients receiving EBRT alone was 3.6 years (95% CI, 3.0–4.2 years) versus 6 years. Cox proportional hazard model revealed decreased risk of death among patients who received brachytherapy in the matched cohort (HR, 0.77; 95% CI, 0.68–0.86). Brachytherapy reduced risk of death among patients in all stage groups, including 1 year (95% CI, 5.2–7.2 years) for patients receiving brachytherapy ($P \leq .001$). Brachytherapy was also associated with a reduction in risk of death for all FIGO stages.

The choice of the brachytherapy modality is based on the residual tumor thickness following pelvic RT. For residual disease measuring <5 mm in thickness, vaginal cylinder brachytherapy is appropriate, whereas for bulky residual tumors, interstitial implants are performed. The most common brachytherapy modalities used in clinical practice are low dose-rate (LDR), high dose-rate (HDR), and pulsed dose-rate delivery.[127] HDR and LDR

intracavitary brachytherapy have comparable local control, survival, and complication rates.[142] For cylinder brachytherapy, the full vaginal length typically receives a cumulative dose of 60 to 65 Gy, while the region of the tumor is boosted an additional 10 to 20 Gy.[143] For interstitial brachytherapy, the cumulative delivered dose ranges from 70 to 85 Gy, and the recommended dose schedules are described elsewhere.[144] For 3D treatment planning, simulation with MRI or fusion of MRI images with CT simulation at the time of interstitial brachytherapy has been reported with favorable outcomes.[145] For CT-based planning, the placement of fiducial markers may be used to demarcate the superior, inferior, and lateral extent of the tumor for contouring purposes. [127]

In a large retrospective multicenter study, IGABT for primary vaginal cancer demonstrated a high local control with acceptable morbidity. The results from this study illustrated that IGABT could play an important role in the treatment of vaginal cancer. This study assessed outcomes following the nowadays standing treatment for primary vaginal cancer with radio(chemo)therapy and IGABT in a multicenter patient cohort. Retrospective data collection included tumor and treatment characteristics of patients treated with CT–MRI-assisted-based IGABT. At a median follow-up of 29 months (interquartile range [IQR], 25–57), 2- and 5-year local control were 86% and 83%; DFS was 73% and 66%, and OS was 79% and 68%, respectively. Univariate analysis showed improved local control in patients with T2–T4 tumors if >80 Gy equivalent dose at 2 Gy (EQD2) α/β10 was delivered to the CTV at the time of brachytherapy.

Ferrigno et al published a report on the comparative outcome of patients with cervical cancer treated with LDR and HDR brachytherapy.[146] In this retrospective analysis, 190 patients were treated with LDR brachytherapy, and 118 patients were treated with HDR brachytherapy.

The OS, DFS, and local control at 5 years were better in the LDR group (69% vs. 55%, P = .007; 73% vs. 56%, P = .002; and 74% vs. 65%; P = .04, respectively) for all stages combined. However, for clinical stages I and II, no differences were seen in OS, DFS, and local control at 5 years between the two groups. For clinical stage III, although OS and DFS at 5 years were better in the LDR than in the HDR group (46% vs. 36%, P = .04 and 49% vs. 37%, P = .03, respectively), the 5-year probability of rectal complications was higher in the LDR group than in the HDR group (16% vs. 8%, P = .03).

Thus, similar outcomes were observed for patients who were in stages I and II treated with either HDR or LDR brachytherapy. Although lower OS and DFS were observed for patients who were stage III treated with HDR brachytherapy, fewer late rectal complications were observed in this group. These findings were probably the result of the relatively low HDR brachytherapy dose delivered at Point A.

For very-early-stage vaginal cancers (<5 mm) not requiring EBRT, intracavitary brachytherapy alone may be used. The LDR data suggest improved outcomes with doses of approximately 60–70 Gy EQD2 to the vaginal surface. For invasive cancers, common HDR fractionation regimens after 45 Gy to pelvis include 4.5 to 5.5 Gy x 5 fx to the HR-CTV.

Either less fractionated or more fractionated regimens may be used, such as 7 Gy x 3 fx or 3 Gy x 9 to 10 fx. Modulation of dose takes into consideration tumor location, extent of disease, response to EBRT, brachytherapy technique (intracavitary or interstitial), relationship to surrounding OARs, as well as other factors. The HDR data are more varied, with total doses in the range of 50 to 60 Gy EQD2. The appropriate dose for each case needs to be individualized.

External Beam Radiation Therapy/Intensity-Modulated Radiation Therapy

Definitive RT, which consists of a combination of EBRT and brachytherapy, has been shown to yield excellent outcomes.[129] The

advantage of RT is the preservation of the vagina as well as other organs. Brachytherapy alone is not recommended for most tumors, even early-stage, due to a high recurrence rate.

Frank et al[129] evaluated the outcomes and describe clinical treatment guidelines for patients with vaginal cancer treated with definitive RT. In this single-institution report, a total of 193 patients with vaginal cancer treated with definitive RT were reviewed to obtain patient information including treatment characteristics and surviving patients were followed for a median of 137 months.

At 5 years, disease-specific survival (DSS) rates were 85% (stage I), 78% (stage II), and 58% (stage III–IVA disease) (P = .0013) and pelvic disease control rates were 86% (stage I), 84% (stage II), and 71% (stage III–IVA) (P = .027). The predominant mode of relapse after definitive RT was locoregional (68% and 83%, respectively, for patients with stages I–II or III–IVA) disease.

A unified approach to techniques and prescription/fractionation schedules for both EBRT and IGABT is required and RetroEMBRACE and EMBRACE I studies have demonstrated that clinical outcome is related to dose prescription and technique. The EMBRACE II study is an interventional and observational multicenter study that aims to benchmark a high level of local, nodal, and systemic control while limiting morbidity, using an advanced target volume selection and contouring protocol for EBRT and a multiparametric brachytherapy dose prescription protocol for brachytherapy, and use of advanced EBRT (IMRT and IGRT) and brachytherapy (intracavitary/interstitial) techniques.[147]

The addition of brachytherapy to external pelvic radiation increases survival in stages III–IV. A retrospective analysis of patients with primary squamous, adenocarcinoma, and adenosquamous carcinoma of the vagina were identified from the Mayo Clinic Cancer Registry (1998–2018) to analyze clinical characteristics and survival of patients with primary vaginal cancer by Yang et al.[148] In a total of 124 patients, primary surgery in stage I–II patients had similar survival outcomes as compared to primary radiation, but postoperative RT rate was 55%. Brachytherapy alone was associated with a high local recurrence rate (80%) in stage I–II patients. The addition of brachytherapy had improved 5-year PFS and DSS compared to EBRT alone in patients with stage III–IVA disease (P < .001).

General recommendations for radiation volumes and doses for both EBRT and brachytherapy are discussed in the algorithm.

External Beam Boost

Intensity-modulated RT is becoming more widely available; however, issues regarding target definition, patient and target immobilization, tissue deformation, toxicity, and reproducibility remain to be validated.[149-156] Dose-escalated IMRT (limiting V55 to below 15 cm^3 and limiting the dose to duodenum) can safely and effectively treat para-aortic nodal disease in gynecologic malignancies reducing the risk of late duodenal toxicity.[157] Among 105 patients with gynecologic primary tumors and treated to a nodal CTV to 45 to 50.4 Gy with a boost to 60 to 66 Gy, only 9 of 105 patients (2 of 38 cervical patients) experienced duodenal toxicity with 3-year actuarial rate of any duodenal toxicity of 11.7%. IMRT technique can reduce acute and chronic GI and hematologic toxicity.

An international, multicenter, phase 2 clinical trial (INTERTECC-2) evaluated acute hematologic and GI toxicity for 83 patients with cervical cancer who received weekly cisplatin concurrently with once-daily IMRT, followed by intracavitary brachytherapy.[158] The primary endpoint was the occurrence of either acute grade ≥3 neutropenia or clinically significant GI toxicity within 30 days of completing chemoradiation therapy. The incidence of any primary event was 26.5% (95% CI, 18.2%–36.9%), and

the incidence of grade ≥3 neutropenia and clinically significant GI toxicity was 19.3% (95% CI, 12.2%–29.0%) and 12.0% (95% CI, 6.7%–20.8%), respectively. Compared with patients treated without image-guided IMRT (n = 48), those treated with image-guided IMRT (n = 35) had a significantly lower incidence of grade ≥3 neutropenia (8.6% vs. 27.1%; 2-sided χ2; *P* = .035).

Several retrospective analyses suggest that prolonged RT treatment duration has an adverse effect on outcome.[159-163] Extending the overall treatment beyond 6 to 8 weeks can result in approximately a 0.5% to 1% decrease in pelvic control and cause specific survival for each extra day of overall treatment time. Thus, although no prospective randomized trials have been performed, it is generally accepted that the entire RT course (including both EBRT and brachytherapy components) should be completed in a timely fashion (within 8 weeks); delays or splits in the radiation treatment should be avoided whenever possible.

Reirradiation

Techniques for re-irradiation may include IORT, intracavitary or interstitial brachytherapy, SBRT, IMRT, or proton therapy.[164-166] Such cases are highly customized and depend on the target, proximity to critical organs, previous RT dose, extent of overlap, and time intervals since prior RT. The appropriate dose for each case needs to be individualized.

IORT is a specialized technique that delivers a single, highly focused dose of radiation to an at-risk tumor bed or isolated unresectable residual disease during an open surgical procedure.[141] It is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such as bowel or other viscera) can be manually displaced from the region at risk. IORT is typically delivered with electrons, brachytherapy, or miniaturized x-ray sources using preformed applicators of variable sizes matched to the surgically defined region at risk, which further constrains the area and depth of radiation exposure to avoid surrounding normal structures. For patients with locoregional recurrence who have received prior EBRT with/without brachytherapy, IORT is recommended as NCCN category 3 with major NCCN disagreement that the intervention is appropriate.

Other techniques for reirradiation may include intracavitary or interstitial brachytherapy, SBRT, IMRT, or proton therapy. Such cases are highly individualized and depend on the target, proximity to critical organs, previous RT dose, extent of overlap, and time intervals since prior RT. The appropriate dose for each case needs to be individualized.

Concurrent Chemoradiation

Based on a small retrospective series and adaptation from cervical cancer, concurrent chemoradiation therapy (CCRT) may be used in vaginal cancer.

In a single-institution report, clinical outcomes in patients with primary vaginal cancer with RT or CCRT were reviewed.[167] A total of 51 patients were treated with RT alone; 20 patients were treated with CCRT, recurrences were analyzed, and OS and DFS rates were estimated. The 3-year OS of the RT group was 56% compared to 76% in the CCRT group (log-rank *P* = .037). The 3-year DFS rate was 43% in the RT group compared to 73% in the CCRT group (log-rank *P* = .011). Twenty-three patients (45%) in the RT group had a relapse at any site compared to 3 (15%) in the CRT group (*P* = .027). Regarding the sites of first relapse, 10 patients (14%) had local only, 4 (6%) had local and regional, 9 (13%) had regional only, 1 (1%) had regional and distant, and 2 (3%) had distant-only relapse. Concurrent chemotherapy should be considered for patients with vaginal cancer.

The adoption rate of CCRT and its survival impact were analyzed using the National Cancer Database (NCDB), which included patients

diagnosed with vaginal cancer who received definitive RT.[168] Of the 13,689 patients identified, 8222 (60.1%) received RT. Of these, 3932 (47.8%) received CCRT and its use increased from 20.8% to 59.1% (1998–2011). Median OS is longer with CCRT compared to radiation alone (56.2 vs. 41.2 months, $P < .0005$). This large, national cohort study emphasized the increased use of CCRT for patients with vaginal cancer and its association with a significant survival improvement. Chemoradiation with brachytherapy is the preferred regimen for patients with vaginal cancer with stage II–IVA disease.

Normal Tissue Considerations

Planning for RT in vaginal cancer must consider the potential impact on surrounding critical structures, such as rectum, bladder, sigmoid, small bowel, and bone. Acute effects (ie, diarrhea, bladder irritation, fatigue) occur to some degree in most patients undergoing radiation and are typically magnified by concurrent chemotherapy. However, acute effects can often be managed with medications and supportive care, and they generally resolve soon after completion of radiation. To avoid treatment-related menopause, ovarian transposition can be considered before pelvic RT in select young patients (<45 years with early-stage disease).[169-171]

Late complications from RT in patients with gynecologic cancer may include potential injury to bladder, rectum, bowel, and pelvic skeletal structures.[172] The risk of major complications (eg, obstruction, fibrosis/necrosis, fistula) is related to the volume, total dose, dose per fraction, and specific intrinsic radiosensitivity of the normal tissue that is irradiated.[173-175] Careful blocking in order to minimize normal tissue exposure while maintaining tumor coverage is critical for optimal outcomes. In addition, patient-related conditions (ie, inflammatory bowel disease, collagen-vascular disease, multiple abdominal/pelvic surgeries, history of pelvic inflammatory disease, diabetes) influence determination of radiation dose and volumes.

For most patients, it is generally accepted that the whole pelvis can tolerate an EBRT dose of 45 to 50 Gy. Gross disease in the parametria or unresected nodes may be treated with tightly contoured external-beam boosts to 65 to 70 Gy. Care should be taken to minimize dose to uninvolved and out-of-field external genitalia when possible but without compromising coverage of the PTV. Brachytherapy to reach 70–80 Gy EQD2 total dose is generally recommended, with lower dose ranges of 70–75 Gy considered in the lower vagina, and 75–80 Gy total dose in the upper vagina. For bulky or poorly responsive disease in the upper vagina, dose escalation ≤85 Gy may be considered. Some clinicians treat the entire vaginal surface to 60 Gy cumulative dose, followed by tumor boost to 70–80 Gy, while others treat only the lesion plus a margin. Careful attention should be paid to dose tolerance of vaginal mucosa. The distal vagina has a lower tolerance than the proximal vagina. Brachytherapy planning is highly individualized and should incorporate information from pre-EBRT and pre-brachytherapy imaging (preferably MRI), clinical drawings, fiducials, and exam findings. Careful understanding of vaginal anatomy and distribution of disease is required. Image-guided brachytherapy is strongly encouraged, with adaptation of volumes as the tumor responds. Tumor extent, location, and response must all be considered when choosing the brachytherapy approach.

Normal tissue dose constraint guidelines for vaginal cancer have been added to the NCCN Guidelines for Vaginal Cancer. Although the suggested dose constraints are provided in the Guidelines, the NCCN Panel recommends that clinicians must balance the risks of normal tissue toxicity with tumor control.

Drug Reactions

Virtually all drugs have the potential to cause adverse reactions, either during or after infusion.[176] In vaginal cancer treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, and paclitaxel. Most of these drug reactions are mild infusion reactions (ie, skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (ie, life-threatening anaphylaxis) can occur.[177,178] In addition, patients can have severe infusion reactions and mild allergic reactions. Infusion reactions are more common with paclitaxel.[179] Allergic reactions (ie, true drug allergies) are more common with platinum agents (eg, cisplatin).[179,180] Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer.[179] Importantly, patients who experienced severe life-threatening reactions should not receive the implicated agent again unless evaluated by an allergist or specialist in drug desensitization. If a mild allergic reaction previously occurred and it is appropriate to readminister the drug, a desensitization regimen is recommended even if the symptoms have resolved. Various desensitization regimens have been published and should be followed.[180-182] Patients must be desensitized with each infusion if they have had a previous reaction. Almost all patients can be desensitized.[176] To maximize safety, patients should be desensitized in the intensive care unit.[176]

Gynecologic Survivorship

Treatment for gynecologic cancer typically involves surgery, chemotherapy, hormone therapy, RT, and/or immunotherapy, which may cause acute, short term, and long-term toxicities. Surgical approaches may be extensive and cause adhesions to form, which in turn may cause pain and contribute to the development of small bowel obstruction, urinary or GI complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a variety of urinary, bowel, and/or sexual effects), and lymphedema. Chemotherapy agents vary, though commonly used regimens may pose a significant risk of neurotoxicity, cardiac toxicity, cognitive dysfunction, and the development of hematologic cancers. 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) and may predispose patients to subsequent cancers of the skin, subcutaneous tissue, and/or underlying organs that are proximal to the radiation field. Use of immunotherapy agents in gynecologic cancers is emerging, and to date, long-term effects of these treatments are unknown.

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). 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 followed by necessary imaging and/or laboratory testing. 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. Post-radiation use of vaginal dilators and moisturizers is recommended. 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). 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. 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.

Best Supportive Care

Patients with refractory systemic cancer warrant a comprehensive coordinated approach involving hospice care, pain consultants, and emotional and spiritual support, individualized to the situation (see the NCCN Guidelines for Palliative Care).

Summary

In summary, vaginal cancer tends to be associated with older age (>60 years). The most common signs and symptoms of vaginal cancer include bleeding, discharge, and urine retention; in some cases, vaginal cancer is identified by rectal symptoms like constipation or blood in the stool. The primary technique to detect vaginal cancer is pelvic examination. Many of the recommendations for staging, treatment, and follow-up of primary vaginal cancer are derived from cervical cancer and they have generalizability to vaginal cancer due to similar tumor biology. If the diagnosis can be made in an early stage of vaginal cancer, then RT is the preferred recommendation, as well as surgery in select patients. EBRT, EBRT with brachytherapy, and CCRT with brachytherapy are recommended in the later stages of the disease. Preventive measures such as HPV vaccination, regular gynecologic examinations, and tests like Pap cytology and cervicography aid in prevention and early diagnosis of the disease.[7] The hope is that immunization against HPV will prevent persistent infection and therefore prevent specific HPV-associated cancers, including vaginal cancer.[8,183,184]

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