

Vaginal Cancer, Version 2.2026

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Vaginal Cancer outline the recommended diagnostic workup, staging considerations, and treatment options for this rare malignancy. Because vaginal cancer is uncommon and shares many biologic and clinical characteristics with cervical cancer, several management recommendations, particularly systemic therapy, are extrapolated from evidence and practices established for cervical cancer. This guideline excerpt summarizes key components of management, including diagnostic evaluation and workup, principles of staging, pathology considerations, radiation therapy principles, and primary treatment recommendations for both early-stage and advanced disease. It also details approaches to manage relapses, including locoregional recurrence and distant metastases, and provides an in-depth overview of systemic therapy recommendations for vaginal cancer.

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Overview

Vaginal cancer is a rare gynecologic malignancy representing 1%–2% of all gynecologic neoplasms.¹ An estimated 8,070 new cases of vaginal and other genital cancers will be diagnosed in the United States in 2025, and 1,950 people are estimated to die of the disease.² Because of the rarity of vaginal cancer, phase III trials have not been performed 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 with nonhysterectomized individuals.⁴ The risk for vaginal cancers is most common in individuals assigned female at birth (AFAB) >70 years of age. Age-standardized incidence rate of vaginal preinvasive neoplasia ranges between 0.5 to 1.3 per 100,000 individuals AFAB (before 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%–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%–70% of all vulvar and vaginal cancers, and in about 85%–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%–72% of cervical, 27%–58% of vulvar, and 46%–77% of vaginal cancers. HPV18 has been detected in 11%–22% of cervical, 2%–10% of vulvar, and 3%–27% of vaginal cancers. HPV16 has been reported to be present in 49%–81% of VaIN 2/3, whereas only 2%–14% of these lesions test positive for HPV18.⁵

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To view disclosures of external relationships for the NCCN Guidelines panel, go to <https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels>

The full NCCN Guidelines for Vaginal Cancer are not printed in this issue of JNCCN. The complete and most recent version of these guidelines is available free of charge at NCCN.org.

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 ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

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All recommendations are category 2A unless otherwise indicated.

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.

PLEASE NOTE

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NCCN CATEGORIES OF PREFERENCE

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other: 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: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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, available at NCCN.org, and <http://smokefree.gov>).

In 2020, 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 nonkeratinizing 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 were discussed among the members of the NCCN Vaginal Cancer panel during the process of developing these guidelines.

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 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 and should include inspection of the vaginal fornices and biopsies of the cervix.

Workup for these patients with suspicious symptoms includes history and physical, which includes collecting sexual history, immunosuppression, prior hysterectomy, smoking history, gynecologic and anorectal symptoms, pelvic examination (bimanual and rectovaginal), cervical evaluation and pap cytology, colposcopy, vulvar evaluation, imaging, CBC, comprehensive metabolic panel, and testing for HPV and HIV in select patients. Due to diverse diagnosis of vaginal cancer, multidisciplinary expertise is recommended (Figure 1).

For detailed surgical staging and imaging recommendations by stage and planned treatment approach, see "Principles of Imaging" and "Staging" in the algorithm (available, in these guidelines, at NCCN.org). Smoking cessation and counseling, as well as HIV testing (especially in younger patients), are recommended. Patients with vaginal cancer and HIV should be referred to an HIV specialist and should be treated for vaginal cancer as per these guidelines. However, modifications to cancer treatment should not be made solely based on HIV status. If indicated, smoking cessation and counseling intervention is recommended. More information can be found in NCCN Guidelines for Smoking Cessation and NCCN Guidelines for Cancer in People with HIV, available at NCCN.org. Patient distress also