Diagnosis and Management of Vaginal Cancer

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Abstract

Primary malignancies of the vagina are rare, comprising only about 1–4% of all gynecologic malignancies. The majority of vaginal cancers are metastases from other sites. Among primary vaginal tumors, squamous cell carcinoma (SCC) is the most common, followed by adenocarcinoma, melanoma, and other rare histologies. Squamous cell carcinomas are frequently associated with chronic human papillomavirus (HPV) infection, whereas adenocarcinomas are associated with in utero diethylstilbestrol (DES) exposure. Vaginal intraepithelial neoplasia (VAIN) is a premalignant condition thought to progress to invasive squamous cell carcinoma if untreated. Vaginal intraepithelial neoplasia is generally asymptomatic and diagnosed by abnormal vaginal cytology followed by vaginal colposcopy and biopsies. Most vaginal cancers present with abnormal vaginal bleeding or a vaginal mass. Diagnosis is made by physical exam and confirmatory biopsy. Treatment of vaginal cancer depends on the primary histology, stage at diagnosis, and patient characteristics. Treatment options include surgical excision, radiation therapy, and chemotherapy. The majority of vaginal cancers are treated with radiation, frequently in combination with chemotherapy. Prognosis varies depending on underlying histology and stage at presentation; however, with advances in radiation techniques, survival rates are similar to those seen in cervical cancer.

Keywords

Vaginal intraepithelial neoplasia (VAIN) • Vaginal squamous cell carcinoma • Vaginal adenocarcinoma • Vaginal melanoma • Vaginal rhabdomyosarcoma

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1 Introduction

Primary malignancies of the vagina are quite rare, comprising only about 1–4% of all gynecologic malignancies (Siegel et al. 2015). In the USA, approximately 4000 women are diagnosed with vaginal cancer each year, and approximately 900 women die of the disease (Siegel et al. 2015). The majority of cancers involving the vagina are actually secondary metastases or direct extensions from other primary sites. In a series of 355 invasive carcinomas involving the vagina, only 58 (16%) represented primary vaginal lesions. Among secondary sites metastatic to the vagina, the cervix was most common (32%), followed by the endometrium (18%), colon and rectum (9%), ovary (6%), vulva (6%), bladder and urethra (4%) (Fu and Reagan 1989).

In this chapter, we will focus on the diagnosis and management of primary vaginal malignant neoplasms and premalignant conditions. Due to the rarity of the disease, most treatment strategies are derived from small retrospective case series and extrapolated from prospective studies for the treatment of cervical and anal cancers. Squamous cell carcinoma is the most common and well-studied histology, representing 65–79% of vaginal cancers in two large cancer registry studies (Creasman et al. 1998; Shah et al. 2009). Adenocarcinoma is the second most common histology representing 9–14% of tumors, followed by melanoma (3–6%) and other rare histologies including mesenchymal, germ cell, neuroendocrine, and hematologic cell types collectively accounting for the remaining 4–15% (Creasman et al. 1998; Shah et al. 2009). The majority of vaginal cancers are treated with radiation, frequently in combination with chemotherapy. Prognosis varies depending on underlying histology and stage at presentation; however, with advances in radiation techniques, survival rates are similar to those seen in cervical cancer.

2 Vaginal Anatomy

The vagina is a fibro-muscular, distensible tube extending from the uterine cervix superiorly to the vestibule of the vagina, vulva, and perineum inferiorly. Embryologically, the vagina is formed by fusion of the urogenital sinus epithelium inferiorly with the mullerian ducts superiorly. Structural support for the vagina includes the cardinal and uterosacral ligaments superiorly and the muscular supports of the pelvic floor including the levator ani, the bulbospongiosus muscle, and urogenital diaphragm. The vagina shares fascial support anteriorly with the bladder and posteriorly with the rectum. Between these attachments, the lateral vaginal wall opens into the paravaginal space. The vaginal fornix describes the recesses around the uterine cervix and can be divided into anterior, posterior, and lateral regions. The posterior fornix is the largest and is separated from the rectum by a fold of peritoneum, forming the pouch of Douglas.

The vaginal wall consists of three layers: the mucosa, the muscularis, and the adventitia. The mucosa is lined by the nonkeratinized stratified squamous epithelium, rich in glycogen and estrogen. There are no glands or crypts in the vagina, and the mucosa is primarily lubricated by cervical glands. Vaginal atrophy, characterized by mucosal thinning and blunting of the vaginal rugae, is common in low estrogen states such as prior to onset of puberty and after menopause. Underlying the epithelial basement membrane is the submucosal layer, highly vascular and rich in lymphatics. The muscularis layer consists of smooth muscle fibers, and adventitia is a thin layer of connective tissue continuous with the adventitia layer of other surrounding organs.

The arterial supply of the upper vagina comes from the internal iliac artery frequently off a trunk shared with the uterine artery, called vaginal

artery, while the middle and lower portions of the vagina are supplied by branches of the middle rectal and internal pudendal arteries. Venous drainage is facilitated by vaginal venous plexuses in the lateral vagina which drain into the internal iliac vein. The vagina is innervated by nerves derived from the inferior hypogastric plexus.

Classically, lymphatic vessels from the upper 2/3 of the vagina drain into the internal iliac and external iliac lymph nodes, while vessels from the lower 1/3 drain into the superficial inguinal lymph nodes via lymphatic channels in the lateral vagina (Plentl and Friedman 1971). Posterior vaginal lesions may also drain into para-rectal nodes (Plentl and Friedman 1971).

3 Natural History

Most data about the natural history of vaginal carcinoma emanates from early case reports where few treatment modalities were available, and many patients presented with advanced disease. In a compilation of early case series, Plentl and Friedman report that of 1204 vaginal cancer cases, 57.2% were located on the posterior wall, 26.9% on the anterior wall, and 15.9% on the lateral wall (Plentl and Friedman 1971). Among 743 cases with data available, 50.7% of tumors were located in the upper 1/3 of the vagina, 18.8% in the middle 1/3, and 30.4% in the lower 1/3. VAIN also has a predilection for the upper vagina, which is thought to be due to an HPV-related field effect in patients with cervical HPV infections.

Vaginal cancers may spread by contiguous growth and local invasion, lymphatic drainage, and hematogenously. Because of closely approximated structures including the urethra, bladder, rectum, and pelvic bones, locally advanced disease is generally symptomatic and carries a high rate of morbidity. Due to the rich lymphatic drainage of the vagina, lymph node metastases occur relatively early in the disease. By contrast, hematogenous dissemination to distant sites, such as the liver, lung, or bone, occurs late in the disease process.

4 Epidemiology

Vaginal squamous cell carcinoma is primarily a disease of older women, with peak incidence between ages 60 and 80 (Creasman et al. 1998; Shah et al. 2009). Vaginal squamous cell carcinoma is considered to be an HPV-related disease and shares many risk factors with other HPV-related squamous cell carcinomas, including prior documented HPV infection (particularly HPV 16), history of cervical or vulvar dysplasia (CIN or VIN), immunosuppression, five or more sexual partners or sexual debut prior to age 17, smoking, and low socioeconomic status (Daling et al. 2002). VAIN and squamous cell carcinomas are strongly associated with a prior history of cervical cancer. Prior radiation therapy (Hellman et al. 2004) and chronic vaginal irritation related to pelvic organ prolapse and pessary use have also been proposed as possible risk factors (Wang et al. 2014).

Vaginal adenocarcinoma is associated with precursor lesions including vaginal adenosis, endometriosis, and mesonephric rests. Vaginal clear cell carcinoma, associated with in utero diethylstilbestrol (DES) exposure is the most commonly described form in the literature. DES is a nonsteroidal estrogen that has been implicated in congenital reproductive tract abnormalities including persistence of vaginal glandular tissue in a condition called vaginal adenosis. In review of registry cases, Herbst reported that among women exposed to DES in utero, the risk of clear cell carcinoma of the vagina or cervix was approximately 1/1000, with age at diagnosis ranged from 7 to 34 years, with peak incidence at age 14–22 (Herbst and Andersond 1990). Vaginal adenosis occurred in 45%, and structural genital tract anomalies in 25%. The incidence of vaginal clear cell carcinoma has declined significantly since the 1990s. Non-DES-related vaginal adenocarcinomas occur in older women, with a median age at diagnosis of 54 (Frank et al. 2007).

A small subset of vaginal cancer has a predilection for the pediatric population. Vaginal rhabdomyosarcoma, also known as sarcoma botryoides, accounts for approximately 4% of

rhabdomyosarcomas, which are the most common tumors in childhood. The median age at presentation is 16.3 months (Magné et al. 2008). Vaginal and cervical yolk sac tumors, also known as endodermal sinus tumors, are another rare vaginal tumor of childhood. Only about 100 cases have been reported in the literature, all diagnosed prior to age 3.

5 Signs and Symptoms

Approximately 15–17% of vaginal cancers are asymptomatic and identified by abnormal cytology or incidental mass on routine pelvic examination (Eddy et al. 1991; Hellman et al. 2004). Abnormal vaginal bleeding is the most commonly reported symptom of invasive carcinoma; however, abnormal vaginal discharge and dysuria are also frequently reported. In the case of more advanced disease, patients may present with pain, the sensation of a mass, or symptoms related to the involvement of adjacent pelvic organs. Tumors involving the bladder may present with urinary incontinence or retention, hematuria, urgency, or frequency. Tumors involving the rectum may present with constipation, tenesmus, or rectal bleeding. Sarcoma botryoides presents with a characteristic edematous, grape-like mass protruding from the vagina.

Vaginal intraepithelial neoplasia (VAIN) is generally asymptomatic, but may present with abnormal vaginal discharge which is often the result of a coincidental vaginitis. Most cases of VAIN are diagnosed after abnormal vaginal cytology in women who have a history of cervical dysplasia

6 Diagnosis

Vaginal cancer should be diagnosed after a thorough focused history and physical exam, careful inspection of the vagina, confirmatory biopsies, and exclusion of more common gynecologic malignancies which may have metastasized to the vaginal mucosa. According to the International Federation of Gynecology and Obstetrics (FIGO) definitions, any vaginal lesion also involving the cervix or the vulva should be classified as a cervical or vulvar primary cancer, respectively (Hacker et al. 2015). Similarly, in women with a prior history of cervical carcinoma, a vaginal carcinoma lesion should not be considered a second primary unless the patient has been without evidence of disease for at least 5 years (Hacker et al. 2015).

Inquiry of clinical history should include symptoms and risk factors associated with vaginal carcinoma and a complete past medical and gynecological history. Physical examination should focus on evaluation of potential metastatic sites, with particular care to palpate the inguinal and supraclavicular lymph nodes, which may be enlarged in advanced disease.

During pelvic examination, the vulva and anus should be carefully inspected for HPV-related lesions, with care to visualize folds of the labia and the vaginal vestibule prior to speculum insertion. The entire vaginal surface should be visualized, which may require an exam under anesthesia in women with locally advanced disease or vaginal stenosis secondary to severe vaginal atrophy or prior radiation. Most vaginal cancers are located in the upper vagina, frequently on the posterior wall. A speculum examination should be performed with care to inspect the anterior and posterior fornix as well as the distal vagina. Lesions in the distal anterior and posterior vagina may be obscured by the blades of the speculum unless the speculum is gently rotated to expose the circumferential surface of the vagina. Small lesions may be difficult to identify in parous or obese women with redundant vaginal folds. In women who have had a prior hysterectomy, lesions also may be concealed by folds of mucosa buried within the vaginal cuff closure. Partial upper vaginectomy may be required to adequately evaluate these patients.

Vaginal cancers are frequently exophytic, papillary appearing tumors, but infiltrating, ulcerative and flat spreading forms are also seen (Morrow and Curtin 1998). Carcinomas arising in the setting of extensive VAIN may be multifocal. Any visible lesions should be evaluated with full-thickness mucosal biopsies. Vaginal cytology

may also be useful to identify cellular atypia, but should not be used alone to evaluate for VAIN or vaginal malignancies. Any woman with a suspicious vaginal lesion who has not had a total hysterectomy should also have consideration of cervical biopsies and endocervical sampling to evaluate for an occult cervical malignancy. Similarly, women with abnormal bleeding and an intact uterus should have an endometrial biopsy or dilation and curettage to evaluate for endometrial cancer. A bimanual exam should be performed to palpate the size and extent of an intravaginal mass and assess for any pelvic masses. This exam should be followed by a rectovaginal exam to identify gross invasion through the rectal mucosa, tumor infiltration of the rectovaginal septum, and parametrial or pelvic sidewall involvement. When locally advanced disease is suspected based on the size and location of the primary tumor, cystourethroscopy and/or proctoscopy are indicated. Biopsies should be obtained if there is any question of mucosal bowel or bladder involvement. Sigmoidoscopy may also be considered for women with large tumors in the posterior vaginal fornix that are suspected to extend into the pelvis.

All patients with abnormal cytology but no grossly visible lesion should be further evaluated with vaginal colposcopy. Some providers advocate colposcopy for all cases of vaginal carcinoma in order to visualize any areas of occult mucosal involvement or associated dysplasia. Colposcopy can be performed in the office during initial examination and may be repeated in the operating room as needed to guide biopsies or excision of lesions identified. Acetic acid solution should be liberally applied to the vagina, and the mucosa should be inspected under magnification using a colposcope. Lugol's iodine solution may be a useful adjunct to identify nonstaining mucosa. Colposcopically abnormal mucosa should be biopsied for diagnosis. When there is a question of high-grade dysplasia versus invasive carcinoma, lesions should be excised, as a large superficial lesion may contain a small focus of deeper invasion that could be missed on biopsy alone. A complete upper vaginectomy may be necessary in order to adequately rule out invasive carcinoma in the setting of multifocal or extensive high-grade VAIN. In a series of sequential upper vaginectomies for VAIN2 or VAIN3 from 1985 to 2004, Indermaur et al. reported that 12/105 (12%) had a previously unsuspected invasive carcinoma (Indermaur et al. 2005).

7 Evaluation and Staging

Similar to cervical cancer, vaginal cancer staging is clinical. Two commonly used staging systems are defined by the International Federation of Gynecology and Obstetrics (FIGO) and American Joint Committee on Cancer (AJCC) TNM staging system (Edge et al. 2010; Hacker et al. 2015). In both systems stage I/T1 describes tumors confined to the vaginal wall; stage II/T2 tumors invade the paravaginal tissues; stage III/T3 involves the pelvic sidewall; stage IV/T4 invades the bladder or rectal mucosa; and distant metastases (M) are labeled stage IVB (Table 1).

Table 1 FIGO stage and 5-year overall survival rates for vaginal cancer

FIGO stage[a]	Definition	Creasman et al. 1998[b] (NCDB data, $n = 4885$)	Shah et al. 2009[c] (SEER data, $n = 2149$)
I	Limited to the vaginal wall	73%	84%
II	Involving subvaginal tissue	58%	75%
III	Pelvic sidewall involvement	36% (stages III and IV)	57% (stages III and IV)
IVA	Bladder or rectum invasion or extension beyond the pelvis		
IVB	Distant metastases		

Compiled from:
[a]Hacker et al. (2015)
[b]Creasman et al. (1998)
[c]Shah et al. (2009)

Lymph node involvement is not directly addressed in the FIGO system, whereas in the AJCC system it is designated by N, and all patients with positive pelvic or inguinal lymph nodes are assigned to N1 (clinical stage III). Metastatic sites (AJCC designation M1) include, but are not limited to, aortic lymph nodes, lungs, liver, bone, and others outside the pelvis. Currently FIGO staging is used more commonly in the treatment of vaginal cancer.

In the FIGO system, studies officially recommended for clinical staging of a tumor are limited in order to preserve consistent labeling across historical data and low resource settings. These studies include pelvic examination, cystoscopy, proctoscopy, chest radiograph, and intravenous pyelogram. Where advanced imaging techniques such as computed tomographic (CT) scans and magnetic resonance imaging (MRI) are available, many providers extrapolate results from these studies into the clinical staging model. Because of its high resolution and ability to discriminate soft tissue plains, MRI of the pelvis can be a particularly useful adjunct to physical exam for determining the extent of tumor invasion into the bladder, rectum, or parametrial tissues. Taylor et al. correlated MRI findings with clinical outcomes in 25 vaginal cancer patients and concluded that MRI could identify 95% of primary lesions and accurately predicted clinical stage (Taylor et al. 2007). Primary vaginal lesions appear with low-intermediate intensity on T1- and hyperintensity on T2-weighted images (Taylor et al. 2007) and may be better visualized if the vagina is instilled with gel during the study to separate and distend the vaginal walls. Positron emission tomography (PET) scans have become a standard tool for evaluating local, nodal, and metastatic disease for initial evaluation and surveillance of cervical cancer. Not surprisingly, PET has also been widely adopted for evaluation of vaginal cancers and has been shown to have superior sensitivity compared with standard CT for detecting both primary vaginal tumors (100% with PET vs. 43% for CT) and nodal metastasis (Lamoreaux et al. 2005).

8 Screening and Prevention

Similar to other rare cancers, screening for vaginal cancer among low-risk populations is not recommended. The American Cancer Society and American Society for Colposcopy and Cervical Pathology (ASCCP) recommend routine vaginal cytology in women who have had a hysterectomy *only* if there is a history of high-grade cervical dysplasia (CIN2/CIN3) (Saslow et al. 2012). Because VAIN and squamous cell carcinomas are closely associated with HPV infection, HPV vaccination campaigns are likely to be the most important strategy to prevent these diseases.

9 Histologic Subtypes and Management

9.1 Vaginal Intraepithelial Neoplasia (VAIN)

Vaginal intraepithelial neoplasia (VAIN), also known as vaginal carcinoma in situ, is a form of squamous cell atypia that is confined to the squamous epithelium of the vagina, without any evidence of invasion. The characteristics of VAIN include nuclear atypia, loss of squamous cell maturation, and the presence of suprabasilar mitoses. Similar to cervical intraepithelial neoplasia (CIN), VAIN1 involves the deepest 1/3 of the epithelium, VAIN2 the deepest 2/3, and VAIN3 the full thickness of the epithelial layer (Fig. 1). VAIN is almost always associated with HPV infection in more than 90% of cases, with HPV 16 being the most common subtype, found in up to 65% of cases of VAIN2/VAIN3 (Smith et al. 2009). The true natural history of VAIN is not known; however, it is considered premalignant because of its association with high-risk HPV types. Invasive squamous cell carcinoma has been identified in up to 12% of vaginectomies performed for VAIN2/VAIN3 (Indermaur et al. 2005).

Treatment strategies for VAIN include observation, local excision, partial or total vaginectomy, ablation with laser vaporization or

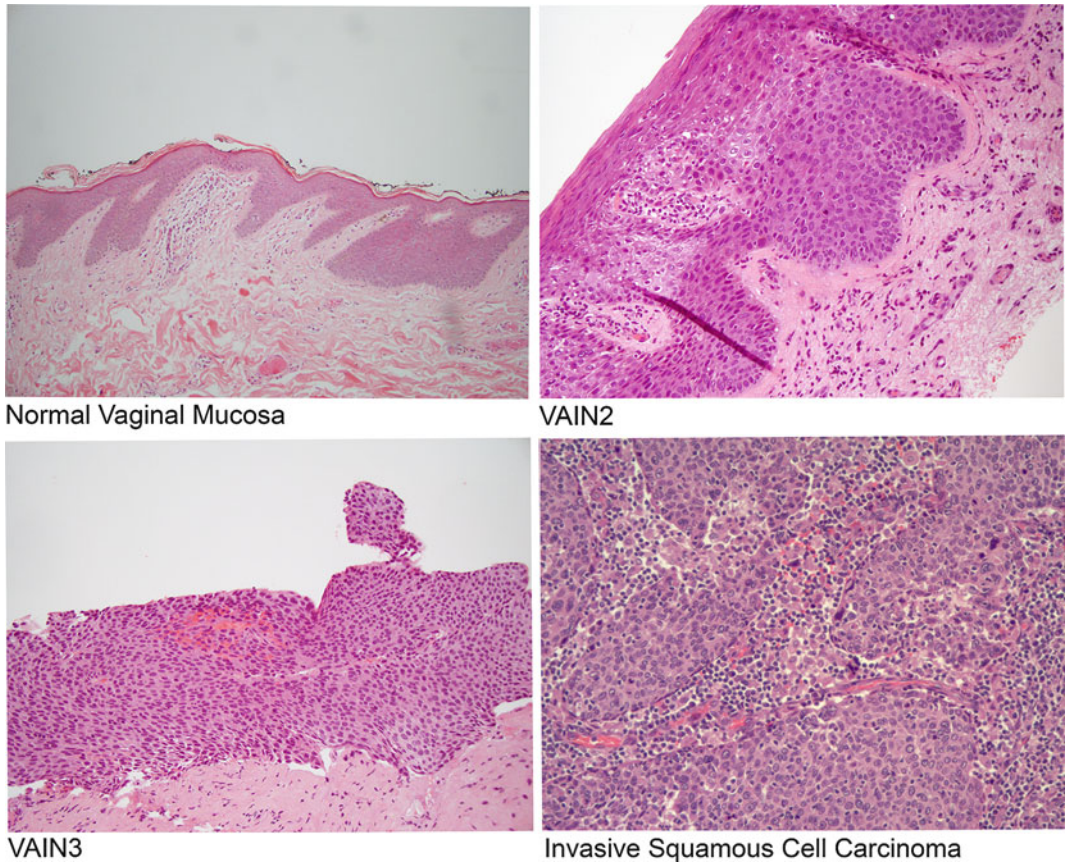

Fig. 1 Vaginal mucosa, high-grade dysplasia, and invasive carcinoma (Ardeshir Hakam 2015)

electrocoagulation, topical 5% fluorouracil, or intracavitary radiation therapy. Observation is limited to the treatment of VAIN1, which is more likely to regress spontaneously. For VAIN2/VAIN3, published disease control rates are similar for all approaches. Most studies consist of small, single institutional case series, and modalities have not been directly compared for efficacy. The choice of therapy should be individualized based on the size, location, and severity of VAIN lesions, as well as the patient's age, general health and life expectancy, desire for sexual function, and prior history of treatment failures. In a significant subset of women, VAIN is chronically persistent and recurrent and may require repeated treatment with multiple modalities. Risk factors for recurrence include multifocal disease, VAIN3, and older age (Dodge et al. 2001). In all cases, invasive carcinoma should be ruled out with adequate sampling biopsies prior to initiating treatment. Treatment strategies are summarized in Table 2.

Surgical excision is the most appropriate management when invasive carcinoma cannot be ruled out, as this is the only approach that will provide tissue for diagnosis. For patients with a focal, well-circumscribed lesion, local excisional colpectomy is the best choice. In more extensive disease, an upper or total vaginectomy may be necessary to obtain adequate margins. These procedures are usually performed vaginally; however upper vaginectomy may require an abdominal approach in some cases, ideally using minimally invasive technique. Vaginectomy can lead to shortening or stenosis of the vagina and loss of sexual function. Reconstructive procedures and

Table 2 Treatment modalities for vaginal intraepithelial neoplasia

Method of treatment	Applications/advantages	Risks and side effects
Surgical excision	Pathologic diagnosis Evaluate for invasive cancer Total vaginectomy provides definitive treatment	Vaginal shortening or stenosis (large excision) Loss of sexual function (vaginectomy) Possible laparotomy or other surgical complications Generally requires anesthesia
Ablation (CO_2 laser or electrocautery)	Preservation of vaginal length Treatment of multifocal or extensive disease Lower rates of sexual dysfunction	Vaginal stenosis may occur Diagnosis of invasive cancer can be delayed Generally requires anesthesia
5-Fluorouracil	Coverage of diffuse or multifocal disease Does not require anesthesia	Vaginal burning Vaginal ulceration Diagnosis of invasive cancer can be delayed May cause vaginal adenosis in rare cases after CO_2 ablation
Imiquimod	Coverage of diffuse or multifocal disease Does not require anesthesia	Vaginal burning Vaginal ulceration Diagnosis of invasive cancer can be delayed
Vaginal estrogen	May augment other treatment modalities	Unproven as monotherapy
Radiation therapy	Usually definitive Effective when other modalities have failed	Vaginal shortening or stenosis Vaginal fibrosis Sexual dysfunction or loss of function Impaired wound healing Radiation cystitis/proctitis Premature menopause/ovarian ablation

skin grafts may be necessary after total vaginectomy. Women with a prior history of radiation therapy are also at increased risk of surgical complications and fistula formation following colpectomy and vaginectomy procedures.

CO_2 laser vaporization is proposed as relatively noninvasive approach that may be useful for large VAIN lesions and multifocal disease in women who want to retain sexual function. The procedure is generally well tolerated, and patients report minimal sexual dysfunction. Ablation procedures should only be performed if an underlying invasive carcinoma can be adequately ruled out and if the entire lesion can be visualized. Lesions that are partially obscured should be excised.

Topical therapies may be useful for women with low-grade persistent VAIN or diffuse, multifocal disease in women who are poor surgical candidates, after invasive carcinoma has been ruled out. The advantage of these modalities is that the entire vaginal surface can be treated, including difficult to access crevices at the vaginal apex. Proposed topical agents include 5-fluorouracil (5FU), imiquimod, and vaginal estrogen. Of these, **5FU** is the best studied. Several 5FU dose regimens have been proposed, but none have been directly compared, and the most commonly used dose is 2 g once weekly for 10–12 weeks (Gurumurthy and Cruickshank 2012). Side effects of vaginal 5FU include burning and vaginal ulceration. Zinc and other barrier creams may be used to protect unaffected areas, and vaginal estrogen may reduce vaginal discomfort. Vaginal columnar metaplasia (adenosis) has been reported when 5FU is administered after prior CO_2 laser ablation, but the significance of this finding is unknown (Paczos et al. 2010; Gurumurthy and Cruickshank 2012). **Imiquimod**, a topical immune modulator, has also been shown to have activity against VAIN in a few small studies. As with 5FU, dosing regimens vary from series to series. Buck et al. reported that 86% of a 42-patient series experience regression of VAIN after a 3-week course of once weekly application of 0.25 g 5%

Table 3 Histologic subtypes of vaginal cancer and their characteristics

	Squamous cell carcinoma	Adenocarcinoma	Melanoma	Rhabdomyosarcoma (sarcoma botryoides)
Epidemiology	Age >60 HPV (HPV 16) History of cervical dysplasia Chronic irritation	Age 14–22 or >60 DES exposure (clear cell) Vaginal adenosis, endometriosis, or mesonephric rests	Age ~60 White, non-Hispanic	Early childhood
Signs/ symptoms	Abnormal pap (ASCUS-HSIL) Vaginal bleeding Vaginal mass	Abnormal pap (AGUS) Vaginal bleeding Vaginal mass	Pigmented lesion Vaginal bleeding Discharge	Grape-like vaginal mass
Treatment modalities	Chemoradiation (EBRT + brachytherapy) Vaginectomy (localized stage I in upper vagina) Pelvic exenteration (central disease)	Conservative surgery Fertility sparing (young patients) Chemoradiation	Surgery Targeted therapies Immunotherapy	Chemotherapy Conservative surgery Radiation
Other histologies: leiomyosarcoma, carcinosarcoma, endometrial stromal sarcoma, yolk sac tumors, neuroendocrine tumor, glassy cell carcinoma, verrucous carcinoma, Wilms tumor, Ewing sarcoma, lymphoma				

HPV human *papillomavirus*, *ASCUS* atypical squamous cells of undetermined significance, *HSIL* high-grade squamous intraepithelial lesion, *AGUS* atypical glandular cells of undetermined significance, *EBRT* external beam radiation therapy

imiquimod cream (Buck and Guth 2003). Side effects of Imiquimod include vaginal burning and irritation. In the Buck et al. series, these side effects were well tolerated, and there were no reports of vaginal ulceration. **Topical estrogen cream** has been advocated as a useful adjunct to all VAIN treatment modalities. Particularly in postmenopausal women with significant vaginal atrophy, topical estrogen therapy may improve detection of VAIN by normalizing adjacent epithelium. Estrogen may also play a role in promoting regression of VAIN (Rhodes et al. 2014).

Radiation therapy is one of the most effective therapies for VAIN, but is less commonly used because of toxicities associated with radiation including vaginal shortening, stenosis, and fibrosis which may interfere with both sexual function and future examinations. Other toxicities include impaired wound healing, risk of inducing premature menopause through ovarian ablation, and radiation cystitis or proctitis. Vaginal intracavitary brachytherapy is most frequently used for definitive treatment of persistent and recurrent VAIN that has failed other modalities, with disease control rates of 86–100% (Gurumurthy and Cruickshank 2012).

Posttreatment surveillance should be similar to follow up schedules in women with cervical dysplasia: every 6 months for 1–2 years and then annually, with vaginal cytology at each visit. HPV testing has not yet been established in the follow-up of VAIN, but may improve the sensitivity of surveillance exams and allow for improved risk stratification and less frequent follow-up.

9.2 Invasive Squamous Cell Carcinoma

(*Summarized in* Table 3)

Invasive squamous cell carcinoma (SCC) shares cytologic features with VAIN, along with evidence of invasion beyond the epithelial basement membrane. Approximately 65% of vaginal SCC is HPV positive (Smith et al. 2009). Similar to VAIN, HPV 16 is the most common HPV type found in vaginal cancer, and p16 staining is highly sensitive and specific for HPV infection in vaginal tumors. SCC may be divided into keratinizing and nonkeratinizing subtypes, and other variants including basaloid, warty, and papillary squamotransitional have also been described.

Vaginal SCC is graded by the degree of differentiation. Grade 1 tumors are keratinizing and generally very similar in appearance to squamous epithelium, with abundant cytoplasm. Grade 2 tumors have less cytoplasm, but are easily recognized as squamous cells, whereas grade 3 tumors are both nonkeratinizing and poorly differentiated. Verrucous carcinoma is a distinct type of SCC also found on the cervix and vulva which presents with a large exophytic mass and is generally very well differentiated and cytologically bland appearing. Verrucous carcinoma spreads locally and is generally treated surgical resection.

Treatment strategies for vaginal SCC may include surgery, radiation, or chemotherapy – alone or in combination. Chemoradiation including a combination of external beam and brachytherapy is currently the most recommended treatment modality for vaginal cancer of all stages. Because of the rare incidence of the disease, there are no phase III clinical trials to guide management. Overall, management strategies are based on the results of small case series; extrapolation of treatment strategies for cervical, vulvar, and anal cancers; and expert opinion. Therapy should be individualized for each patient based on the stage of disease, size and location of the tumor, and personal goals for vaginal function. Whenever possible, patients should be referred to tertiary centers to receive care from providers experienced in treating vaginal cancers.

Surgery has limited utility in the treatment of vaginal cancer because of the close proximity of other organs including the bladder and rectum making it nearly impossible to obtain adequate margins with organ-sparing approach, especially when the tumor has invaded beyond the vaginal mucosa. In the 2015 FIGO Cancer Report, Hacker et al. recommend only four situations in which surgery may be useful (Hacker et al. 2015):

1. Patients with stage I disease located in the upper posterior vagina: When a negative tumor margin of at least 1 cm can be obtained, and an adequate pelvic lymph node dissection performed, patients with small stage I tumors may benefit from radical upper vaginectomy (and hysterectomy if the uterus is in situ).
2. Ovarian transposition prior to radiation therapy for young patients. The authors note that debulking of large primary tumors and/or pelvic nodes larger than 2 cm in diameter may be performed at the time of this procedure.
3. Patients with locally advanced, stage IVA tumors may benefit from primary pelvic exenteration, but should also have a pelvic lymphadenectomy and consideration of bilateral groin dissection. This approach may also be combined with preoperative radiation therapy.
4. Patients with a central recurrence following primary radiation therapy should be offered pelvic exenteration if there is no evidence of distant metastases.

Surgical case series report 5-year overall survival rates of 56–90% for patients with stage I disease treated with partial or total vaginectomy (Davis et al. 1991; Creasman et al. 1998; Ling et al. 2008; Di Donato et al. 2012). Laparoscopic radical vaginectomy with neovagina construction has also been described with excellent overall survival and patient satisfaction. Cancer registry-based studies suggest a survival advantage for patients who are treated surgically when compared with radiation therapy (Ling et al. 2008). Creasman et al. report a 5-year survival rate of 90% for women with stage I disease in the National Cancer Data Base treated with surgery, compared with 63% for women who received radiation therapy alone and 79% for women who received combined surgery and radiation therapy (Creasman et al. 1998). Similarly, Shah et al. also reported a trend toward improved survival in the SEER database for women with stage I disease treated by primary surgery; however, differences in the hazard ratios were only statistically significant when surgery was compared with no treatment for stage I disease (Shah et al. 2009). Trends toward improved survival with surgical management have also been reported for women with stage II disease, but these are not statistically significant, and survival rates are lower overall when compared to women with stage I disease.

In general, improved survival among women treated with primary surgery likely reflects careful selection criteria biased toward women with small, superficial tumors and little comorbidity. The true advantage of primary surgery for patients with early-stage vaginal cancer is preservation of ovarian and sexual function and avoidance of other radiation-related toxicities.

For women with locally advanced disease, anterior, posterior, or total pelvic exenteration is necessary in order to achieve adequate margins around the tumor. Eddy et al. reported 50% 5-year survival among six patients with stage IVA disease who underwent pelvic exenteration following preoperative radiation (Eddy et al. 1991). In general, exenteration should only be offered to patients who have a reasonable chance of long-term survival after the procedure. Preoperative evaluation should include efforts to rule out pelvic sidewall involvement or nodal and distant metastases. Most surgeons advocate beginning the procedure with exploratory laparotomy and pelvic lymphadenectomy to evaluate for peritoneal or nodal disease prior to beginning the exenteration.

Radiation therapy techniques may include intracavitary or interstitial brachytherapy, external beam radiation therapy (EBRT), or intensity-modulated radiation therapy (IMRT). Practical considerations in the selection of radiation modality, dosing, and technique are summarized in the American Brachytherapy Society consensus guidelines and American College of Radiology Appropriateness Criteria for the management of vaginal cancer (Beriwal et al. 2012; Lee et al. 2013). Because of the high rate of local recurrence and lymph node involvement, most vaginal cancers should be treated with a combination of EBRT and brachytherapy.

Most vaginal cancers are treated with pelvic EBRT to a dose of 45–50.4Gy in 25–28 fractions, followed by a boost to a cumulative dose of approximately 70Gy to the primary tumor site. The clinical target volume includes the gross tumor volume with a 1–2 cm margin, the entire vagina and paravaginal/parametrial tissues out to the pelvic sidewalls, and the bilateral pelvic lymph nodes, which generally correspond to the L5/S1 interspace. For tumors involving the middle or distal 1/3 of the vagina, inguinal nodes should also be included (Yeh et al. 2001). When pelvic lymph nodes are known to be involved, or bulky para-aortic nodes are present on pretreatment imaging studies, extended field coverage of the para-aortic region may be necessary.

The boost to the primary tumor site may be accomplished through brachytherapy or IMRT or a combination. Selection of brachytherapy technique depends on the residual tumor thickness following EBRT. Vaginal cylinder brachytherapy is appropriate for residual disease mainly confined to the mucosa. Tandem and ovoids are typically used for women who have an intact uterus. When the depth of tumor involvement is greater than 5 mm, interstitial implants are required to adequately provide a definitive dose to the entire tumor. Interstitial applicator placement is usually done with epidural anesthesia in order to provide adequate pain control during the procedure and therapy. Laparoscopy or laparotomy may be necessary for appropriate interstitial catheter placement in large tumors in order to prevent inadvertent injury to the bowel. Marker seeds of fiducial gold, platinum, or carbon fiber can be used to define the extent of gross disease. Both low and high dose rate (LDR and HDR) protocols have been reported for the treatment of vaginal cancer, and neither has been definitively shown to be superior. There are fewer studies describing HDR; however, the advantage of this dose schedule is fewer fractions, and rather than continuous radiation dosing requiring radiation precautions, HDR protocols allow for visits and nursing care in between treatments (Beriwal et al. 2012).

Among radiation therapy series of more than ten patients, 5-year disease-specific survival ranges from 36 to 100% for stage I disease, 31 to 80% for stage II disease, 8 to 80% for stage III disease, and 0 to 40% for stage IV disease (Di Donato et al. 2012). The range of survival rates likely reflects differences in radiation protocol as well as differences in the characteristics of each tumor.

Concurrent chemoradiation therapy has become the standard of care for locally advanced cervical cancer and has been increasingly adopted as the primary treatment strategy for most vaginal

cancers (Lee et al. 2013). In small series, chemotherapeutics including 5FU, mitomycin C, and cisplatin with concurrent radiation therapy resulted in 5-year survival rates of approximately 65% (Di Donato et al. 2012). Some authors report locoregional recurrence rates as high as 61% following chemoradiation (Roberts et al. 1991), but these reports are difficult to interpret due to variations in stage and tumor size among studies. In the largest single institution report, Miyamoto et al. present a significantly lower recurrence rate (15% vs. 45%, $p = 0.027$) for 20 patients with stage I–IV disease who received chemoradiation (mainly weekly cisplatin) compared with 51 patients who received radiation therapy alone (Miyamoto and Viswanathan 2013). Recently, a large National Cancer Data Base study by Rajagopalan et al. found that 48.6% of 8086 patients who received radiation also received concurrent chemotherapy. Concurrent chemoradiation therapy was significantly associated with improved 5-year overall survival in all stages and for the entire cohort (48.8% for chemoradiation vs. 41.9% for radiation alone). Median overall survival was also significantly increased for all stages of disease when compared with patients who received radiation alone (109 vs. 85 months for stage I, 85.8 vs. 41.7 months for stage II, 43 vs. 19.9 months for stage III, and 18.5 vs. 9 months for stage IV) (Rajagopalan et al. 2014).

Neoadjuvant chemotherapy prior to radical surgery has also been advocated in patients with stage II disease. Panici et al. describe 11 patients who received 3 cycles of cisplatin and paclitaxel followed by radical surgery. In this series, 27% had a complete response and 64% had a partial response prior to surgery, and 73% were disease-free at a median follow-up of 75 months (Panici et al. 2008).

Posttreatment surveillance for vaginal cancer should follow Society of Gynecologic Oncology guidelines (Salani et al. 2011). For high-risk patients (those who were treated with chemotherapy, radiation, or surgery followed by adjuvant therapy or who had advanced disease), a focused history and careful exam should be performed every 3 months for the first 2 years after completing therapy and then every 6 months until 5 years without evidence of disease, after which visits can be repeated annually. Low-risk patients who have stage I disease and were treated by surgery alone may follow up every 6 months for the first 2 years and then annually. Vaginal cytology should be obtained annually to screen for microscopic recurrence, and any cytologic abnormalities should be evaluated with colposcopy. Symptoms such as vaginal bleeding or discharge, pelvic or abdominal pain, new palpable mass, or change in bowel or bladder habits should prompt a CT abdomen pelvis or PET CT to assess for recurrence. There is no evidence to support routine imaging in the absence of symptoms.

Treatment complications affecting vaginal function and the lower urinary and GI tracts are the most common due to the close proximity of vaginal cancers to these pelvic structures. Radiation-related toxicity to the pelvic organs may include radiation cystitis or proctitis and vesicovaginal or rectovaginal fistula. Vesicovaginal and rectovaginal fistulas have also been reported as a complication of radical surgery. Vaginal radiation toxicity includes acute vaginitis, vaginal stricture, vaginal stenosis, or, rarely, vaginal necrosis. In series reporting rates of toxicity, the incidence of grade 2 complications has been reported to be 15–25% (Gadducci et al. 2015). Factors that increase risk of complications include older age, smoking, medical comorbidities affecting vascular profusion and healing such as diabetes and hypertension, and prior pelvic surgery.

Vaginal stricture and stenosis can be reduced with a combination of topical estrogen cream and dilator use. Women who are sexually active should continue to have intercourse on a regular basis if tolerated. Sexual dysfunction following treatment for vaginal cancer is likely multifactorial, and alterations in body image are common.

Loss of fertility and premature menopause are important considerations in the treatment of young women. We recommend that women of reproductive age be offered consultation with reproductive endocrinology regarding fertility preservation options such as oocyte or embryo cryopreservation prior to initiating therapy for vaginal cancer. Ovarian transposition to the

anterior abdominal wall may reduce the likelihood of radiation-induced menopause and should be considered for some young patients.

Patterns and rates of recurrence vary with initial stage at diagnosis. For stage I disease, the recurrence risk is approximately 10–20%, compared with 30–40% for stage II, and 50–70% for stage III and IV (Davis et al. 1991; Chyle et al. 1996; Perez et al. 1999; Tabata et al. 2002). Among patients with stage I disease, locoregional recurrence is far more common, whereas patients with advanced locoregional disease at the time of diagnosis also have higher rates of both persistent disease and new distant metastases, which may occur in up to 47% of patient (Perez et al. 1999; Tabata et al. 2002). Recurrent disease portends a very poor prognosis, with a 5-year survival rate of only 12% (Chyle et al. 1996).

As in the primary setting, salvage treatment strategies include surgical resection, radiation, and chemotherapy. Patients with stage I disease who did not receive radiation initially may be may receive radiation therapy with curative intent. Radiation protocols in this setting are similar to those used at the time of diagnosis and should include EBRT for empiric coverage of pelvic lymph nodes. Recurrences in the distal 1/3 of the vagina should also be treated with empiric sterilization of the bilateral groins. Similarly, in patients with a prior history of radiation, radiation may still be a reasonable option for disease outside the previously radiated field. Patients who have previously received chemoradiation present a therapeutic challenge because bone marrow reserves have been depleted. Women with local recurrence limited to the central pelvis should be offered pelvic exenteration, which offers the only path to long-term disease-free survival, particularly among patients who have failed definitive radiation.

Distant metastases are best treated with systemic chemotherapy, palliative radiation if focal in nature, or best supportive care. Few studies evaluating chemotherapy for recurrent vaginal cancer exist, and most report a poor response to therapy. In a phase II trial presented by Thigpen et al. of the Gynecologic Oncology Group (GOG 26C), only 1/22 women experienced a complete response to cisplatin 50 mg/m^2 given every 3 weeks. Combination therapy appears to be similarly ineffective. In a study of combination of bleomycin, vincristine (Oncovin), mitomycin C, and cisplatin (BOMP), only 1/15 women treated for recurrent disease experienced a response, compared with 5/6 treated in the primary setting (Belinson et al. 1985). For this reason, many patients who are not candidates for exenteration pursue palliative care.

Prognosis has improved with advances in radiation and chemotherapy and particularly with adoption of chemoradiation (Rajagopalan et al. 2014). In a SEER database study by Shah et al. in 2009, stage is the most important predictor of prognosis. A summary of survival rates by stage at diagnosis is provided in Table 1. Other factors linked to shorter overall survival in large cancer registry studies include larger tumor size (>4 cm), lymph node involvement, and older age (Creasman et al. 1998; Shah et al. 2009; Rajagopalan et al. 2014; Gadducci et al. 2015).

9.3 Adenocarcinomas

(*Summarized in* Table 3)

As discussed earlier in this chapter, most vaginal adenocarcinomas reported in the literature are DES-related clear cell carcinomas occurring in adolescents and young women. The prognosis of vaginal clear cell carcinoma is better than for squamous cell carcinoma, with 5-year survival rates of 92% for stage I and 83% for stage II disease (Senekjian et al. 1987, 1988). In contrast, non-DES-related vaginal adenocarcinomas carry a relatively poor prognosis. In a series from MD Anderson, the median age at diagnosis was 54 and 5-year survival of only 34%, compared with 58% among squamous cell carcinoma patients at the same institution (Frank et al. 2007). Both DES-related and non-DES-related adenocarcinomas are treated similarly to vaginal squamous cell carcinoma. The management of adolescent and young women should include efforts to preserve fertility and sexual function when possible. When a tumor is too large for local excision and radiation is planned, laparoscopic ovarian

transposition should be considered to reduce risk of premature menopause.

9.4 Melanoma

(*Summarized in* Table 3)

Primary vaginal melanoma is the third most common primary malignancy of the vagina, representing 3–6% of all vaginal cancers (Creasman et al. 1998; Shah et al. 2009) and only approximately 1% of all melanomas. Vaginal melanomas most often present as a pigmented or ulcerated lesion in the distal 1/3 of the vagina. Amelanotic lesions have also been described and can be mistaken for squamous cell carcinoma. Immunohistochemistry staining for S-100, HMB45, or Melan-A may be helpful in confirming the diagnosis. The average age at diagnosis is approximately 60, and the majority of patients are white non-Hispanic (Leitao et al. 2014).

The prognosis of vaginal melanoma is very poor, with 5-year overall survival of 5–20% (Creasman et al. 1998; Leitao et al. 2014). Survival for vaginal melanoma is also poor compared to melanomas arising in other sites, likely due to diagnosis at later stages of disease. Melanomas are classically thought to be resistant to radiation, and few traditional systemic chemotherapies have been shown to be active. As a result, surgical resection is the mainstay of therapy for vaginal melanoma, with clear surgical margins being the most important determinant of disease control. Acceptable clinical margins for melanoma are 0.5 cm for melanoma in situ, 1 cm for Breslow thickness less than or equal to 2 mm (AJCC T1 or T2 tumors), and 2 cm for Breslow thickness greater than 2 mm (Garbe et al. 2010). Breslow thickness has not been evaluated for vaginal melanoma, and FIGO staging of vaginal cancer is frequently used. Pelvic exenteration has not demonstrated superior survival compared with wide local excision. Even though sentinel lymph node dissection (SLND) is associated with improved survival in cutaneous melanoma, it has not been widely adopted or evaluated in vaginal melanoma cases. Adjuvant radiation using a similar approach to that used for vaginal squamous cell carcinoma has also been reported, with the possibility of cure. Preoperative radiation can also be considered as a way to improve the chance of complete resection for larger tumors.

Treatment should be approached with consultation with a melanoma specialist at a tertiary center whenever possible. Traditional chemotherapeutics have not been demonstrated to improve overall survival, but there is promising data supporting combination of chemotherapy with targeted agents and immunotherapies. While targeted therapies have not been formally evaluated for primary vaginal melanoma, the BRAF inhibitor vemurafenib and immune modulator ipilimumab have yielded promising results in the melanoma field. In light of recent developments and rapidly improving outcomes using novel agents, women with vaginal melanoma should be encouraged to consider clinical trial participation when such opportunities are available.

9.5 Mesenchymal Tumors

Vaginal leiomyosarcoma, a bulky, rapidly growing smooth muscle tumor with a high mitotic index, is the most common mesenchymal tumor of the vagina in adults, but is extremely rare in general. Radical surgical resection offers the best chance of cure, but 5-year overall survival is only 36% (Peters et al. 1985). **Vaginal carcinosarcoma and primary vaginal endometrial stromal sarcoma** have also been reported. Treatment of these tumors is generally extrapolated from strategies employed for the corresponding uterine primaries.

Embryonal rhabdomyosarcoma (sarcoma botryoides, summarized in Table 3**)** is characterized by the presence of cross-striated rhabdomyoblasts. This rare tumor has been treated with radical surgery including pelvic exenteration in the past, but is now more commonly treated with chemotherapy in combination with more conservative surgery and radiation. The Intergroup Rhabdomyosarcoma Study Group (IRSG) has conducted four clinical trials from 1972 to 1997, including all tumor sites that are used to guide therapy and is now in the process of

a fifth study (Raney et al. 2001). The IRSG classifies tumors into four groups: (I) localized disease that is completely excised with no microscopic residual tumor; (II) complete gross resection of disease with microscopic residual disease, including regional disease with positive lymph nodes; (III) incomplete resection with gross residual disease; and (IV) distant metastases. In the IRS-I through IRS-IV studies, patients in groups I–III received a combination of vincristine, actinomycin D, and cyclophosphamide (VAC) for 12 months sometimes in combinations with ifosfamide, or etoposide, and patients in group IV were randomized to receive vincristine and melphalan (VM) or ifosfamide and doxorubicin (ID) followed by VAC and radiation therapy.

9.6 Other Histologies

Rare variants of vaginal cancer have been reported including primary vaginal lymphoma, Wilms tumor, and Ewing sarcoma, as well as germ cell tumors including childhood vaginal endodermal sinus tumors and variants of epithelial carcinomas such as glassy cell and small cell neuroendocrine carcinomas. Treatment of such variants should be individualized and may include elements of management for vaginal cancer combined with therapies adapted for similar histologies at more common disease sites.

10 Summary

Primary vaginal cancer is a rare entity. Squamous cell carcinoma is the most commonly seen histology affecting women in their sixth and seventh decade of life. Most, but not all, squamous cell carcinomas of the vagina are related to HPV infection. Majority of women are asymptomatic or present with vaginal bleeding or a vaginal mass. The diagnosis and staging are accomplished primarily through physical exam, with confirmatory biopsies, although PET and MRI studies are likely to have an increasing role in predicting prognosis and determining optimal treatment. Radiation is the mainstay of therapy except in select cases of focal, early-stage disease or central recurrences. With the introduction of chemoradiation, overall survival approaches rates seen in cervical cancer. Because of the rarity of this disease, there is no recommended screening; however HPV vaccination efforts hold promise for reducing the incidence of this disease in the future.

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