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Squamous Cell Carcinoma of the Vagina

Ferhat Cetin and Özer Birge

Abstract

Vaginal cancer accounts for approximately 4000 cases and over 900 deaths annually. About 1 in 100,000 women will be diagnosed with in situ or invasive vaginal cancer (typically of squamous cell histology). The mean age at diagnosis of squamous cell carcinoma, the most common histologic type of vaginal cancer, is approximately 60 years. However, the disease is seen occasionally in women in their 20s and 30s. Squamous carcinoma is more common as the age of the patient increases. Vaginal cancer is a disease in which malignant (cancer) cells form in the vagina. Vaginal cancer is staged in three ways, based on how far the tumor has progressed in the vagina, whether it has spread to the lymph nodes, and whether it has spread to other parts of the body. These three categories are called T (tumor), N (nodes), and M (whether it has metastasized or spread). Surgery is the most common treatment of vaginal cancer. The surgical procedures used are laser surgery (uses a laser beam as a knife to make bloodless cuts in tissue or to remove a surface lesion such as a tumor); Wide local excision (takes out cancer and some of the healthy tissue around it); Vaginectomy (Surgery to remove all or part of the vagina).

Keywords: human papillomavirus, primary vaginal cancer, squamous cell carcinoma, vaginal bleeding

1. Introduction

Primary vaginal cancer is less prevalent than uterine cancer of the endometrium, ovary, and cervix, but vaginal cancer is more common than vulvar cancer in the United States [1]. Most vaginal tumors are squamous cell carcinomas, but melanomas, sarcomas, adenocarcinomas, and other histologic types also occur. Although primary vaginal cancer is rare, metastasis to the vagina or local spread from adjacent gynecologic or non-gynecologic organs or systems is not uncommon.

In summary, most vaginal malignancies are metastatic and can often arise from the endometrium, cervix, vulva, ovaries, breast, rectum, and kidney [2–5]. Direct spread (e.g., cervix, vulva, endometrium) or lymphatic or hematogenous spread (e.g., breast, ovary, kidney) can cause vaginal metastases.

In situ or invasive vaginal cancer will be diagnosed in approximately one in every 100,000 women (typically squamous cell histology) [6, 7]. Squamous cell carcinoma, the most frequent histologic form of vaginal cancer, is mainly diagnosed in women in

their 60s and 70s, while it can also occur in women in their 20s and 30s. Squamous cell carcinoma occurs more frequently as the patient ages [6].

Human papillomavirus (HPV) infection is thought to be the cause of the majority of vaginal cancer cases, as well as cervical, uterine cancer [8]. In a case-control study, more than half of 156 women with in situ or invasive vaginal cancer tested positive for antibodies to HPV 16 or 18 subtypes [9]. As a result, vaginal cancer and cervical neoplasia share the same risk factors. Specifically, the risk increases with more than one sexual partner over a lifetime, early age at first sexual intercourse, if you still smoke, low socioeconomic status, and various other infections that cause immunosuppression [9, 10].

There was evidence that some high-grade vulvar and vaginal intraepithelial neoplasms are monoclonal lesions derived from the high-grade or malignant disease of the cervix [11]. A retrospective cohort study of over 130,000 women found that women with cervical intraepithelial neoplasia 3 (CIN 3) had a significantly higher risk of developing vaginal cancer than women in the same population and time interval (incidence rate 6.8, 95% CI 5.6–8.2) [12]. A fourfold or higher risk was found up to 25 years after a CIN 3 diagnosis. Similarly, 30% of all women with in situ or invasive vaginal disease had previously been treated for an anogenital tumor (primarily cervical), and 17 out of 25 (70%) invasive cancer biopsy specimens tested positive for HPV type 16/18 DNA in one case series. Similarly, 51 of 153 women with vaginal cancer treated at Princess Margaret Hospital had pre-existing gynecological malignancies, 34 of whom had cervical uteri cancer, and it is recommended that when each type of cancer is detected, the cervix uteri, vagina, and vulvar region be evaluated together [13].

2. Clinical findings

The most prevalent clinical manifestation of vaginal cancer is vaginal bleeding. Many women are asymptomatic. Vaginal bleeding associated with vaginal cancer is typically postcoital or postmenopausal. Any unplanned vaginal bleeding should be investigated to determine if the source is vaginal. There may also be a watery, bloody, or foul-smelling discharge from the vagina [14–16].

The patient may also notice a vaginal mass. Other possible symptoms are related to local spread of the disease, urinary symptoms (e.g., frequency, dysuria, hematuria), or gastrointestinal symptoms (e.g., tenesmus, constipation, melena) [14–16]. Pelvic pain caused by the spread of the disease outside the vagina occurs in 5 percent of patients.

At the time of diagnosis, up to 20% of women have no clinical complaints and are asymptomatic [17–19]. These vaginal malignancies might be discovered incidentally during a pelvic examination or due to cytological screening for cervical cancer.

3. Diagnostic evaluation

Evaluation using pelvic examination, vaginal cytology, and colposcopic or direct vaginal biopsy are the essential parts of diagnostic evaluation.

Questions about the symptoms of vaginal cancer should be included. A gynecologic history, including a history of neoplasms of the cervix or vulvar neoplasia, should be obtained, as a history of other gynecologic malignancies may exclude a diagnosis of vaginal cancer. Medical, surgical, and medication history should be obtained. This should include the evaluation of medical comorbidities that may influence treatment decisions.

A pelvic and physical examination is carried out. The vagina should be extensively checked with the speculum, including the view of the entire periphery and fornix by shifting the speculum position. Any abnormal site or mass should be biopsied. Palpation of the vaginal walls for masses and evaluation of other pelvic masses should be included in a bimanual examination. The inguinal region should be palpated to assess enlarged pathological lymph nodes.

If the lesion is small and located in the lower two-thirds of the vagina, it may be missed on initial examination. On visual inspection of the vagina, the anterior and posterior blades of the speculum obscure this area, so the tumor may be missed unless the vagina is examined when the speculum is removed or the lesion is palpated on bimanual examination. A detailed colposcopic examination is recommended for macroscopic lesions or lesions that cannot be seen with the naked eye.

The rectovaginal examination is also recommended to assess parametrial and pelvic sidewall involvement, as well as probable rectal involvement.

The most prevalent site of primary vaginal carcinoma is the posterior wall of the upper third of the vagina. According to review research, more than half of the tumors in the upper, middle, and lower thirds of the vaginal wall originated in the posterior vaginal wall in 50, 20, and 30% of cases, respectively [7, 20]. A mass, plaque, or ulcer can all be signs of a lesion. To assess metastatic disease, a focused physical examination is conducted. The inguinal region, in particular, should be checked for pathologically enlarged lymph nodes.

A vaginal cytology specimen should be obtained during the pelvic examination. Twenty percent of vaginal cancers are discovered incidentally during cytology screening for cervical cancer [21].

If a lesion cannot be visualized and cytology results are abnormal, acetic acid colposcopy of the cervix and vagina should be performed, followed by Lugol's iodine staining. If a large lesion is visible, some specialists additionally recommend vaginal colposcopy to evaluate the rest of the vagina.

Biopsy of abnormal areas of the vagina in the office may be performed with punch forceps (Baker or Keyes) or cervical biopsy forceps (Tischler or Burke). Examination under anesthesia may be required for examination and biopsy in women with the significant vaginal stricture that prevents adequate office examination, older adult women, or if cystoscopy and proctoscopy are required for clinical staging.

The only imaging studies part of the International Federation of Gynecology and Obstetrics (FIGO) staging for vaginal cancer are chest and skeletal radiographs.

Modern imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), and 18-fluoro-2-deoxyglucose-positron emission tomography and CT (FDG-PET/CT), can help plan treatment. MRI may help determine the size and local extent of the primary vaginal tumor [22, 23]. T2 imaging is usually the best way to see vaginal tumors, and dripping gel into the vaginal canal to expand the vaginal walls can help visualize and evaluate the tumor's thickness. Primary vaginal tumors and abnormal lymph nodes can also be assessed using FDG-PET [24].

4. Diagnosis

Vaginal cancer is a histologic diagnosis based on vaginal biopsy and the absence of a history of gynecologic malignancy may better identify the vaginal disease as recurrent cancer rather than a new primary disease.

4.1 Differential diagnosis

The first step in determining the cause of vaginal bleeding is to rule out bleeding from other areas of the genital tract. A pelvic examination is often used to accomplish this.

Menopausal women may experience vaginal bleeding due to vaginal atrophy. Bleeding can also be caused by a vaginal infection, inflammation, or trauma. A dermatological condition occasionally causes vaginal bleeding (e.g., toxic epidermal necrolysis). Bleeding from these etiologies may result in focal bleeding from a fissure or laceration, which is not usually the case with vaginal cancer. Or there may be ulceration or extensive bleeding, which can also occur with vaginal cancer. A vaginal mass may be benign, such as cysts of the ductus Gartner, vaginal polyps, vaginal adenosis, endometriosis, or dermoid cysts (rare) [25].

4.2 Histopathology

Primary vaginal tumors form a heterogeneous group of malignancies. They may be multicentric and involve many areas, so the entire vaginal mucosa is at risk and should be examined.

The majority of vaginal cancers are squamous cell carcinomas. As previously stated, the average age at diagnosis for squamous cell carcinomas is around 60 years [26]. Tumors can be nodular, ulcerative, indurated, endophytic, or exophytic in general. They resemble squamous cell tumors in other regions histologically. Vaginal cancer is also associated with the human papillomavirus (HPV). The vaginal epithelium, on the other hand, is more stable than the cervical epithelium, which undergoes constant metaplasia and is hence less susceptible to oncogenic viruses [27].

Verrucous carcinoma is an uncommon type of vaginal squamous cell carcinoma that is well-differentiated and has a small probability of becoming malignant [28]. It is usually a large, warty, fungal mass that is locally aggressive but rarely metastasizes. Histologically, it consists of large papillary sheets covered with dense keratin. The deep margin forms a driving edge of well-aligned rete ridges, in contrast to the well-demarcated margins of benign condyloma acuminata.

4.3 Staging

A clinical staging system for vaginal cancer is used by the International Federation of Gynecology and Obstetrics (FIGO) and Tumor, Node, and Metastasis (TNM) [29–31].

Physical examination, cystoscopy, proctoscopy, and chest and skeletal radiographs are used to determine clinical staging. The results of biopsy or fine-needle aspiration of inguinal/femoral nodes or other nodules may be included in the clinical stage. In addition to clinical staging data, information from the resected specimen, including pelvic and peritoneal lymph nodes, will be used as indicated by the TNM system.

In a review of five series with 1375 cases of vaginal cancer, patients were differentiated according to FIGO stage: stage I (26%), stage II (37%), stage III (24%), and stage IV (13%) [32].

Vaginal tumors can spread locally and in various ways systemically:

- Direct extension to the soft tissue structures of the pelvis: parameters, bladder, urethra, and rectum. Eventually, the bony pelvis may also be affected.

- Lymphatic spread to the pelvic and para-aortic lymph nodes. The lymphatic drainage of the upper vagina connects with the cervix and continues first to the pelvic nodes and then to the paraaortic nodes. In comparison, the lymphatics of the distal third of the vagina drain first to the inguinal and femoral nodes and secondarily to the pelvic nodes.
- Hematogenous spread to other organs, including lungs, liver, and bone, is usually seen late and in histopathologically rare lesions.

4.4 Treatment

Because of its rarity, no randomized trials describe the treatment of vaginal cancer. Instead, the treatment approach of cervical and anal cancer is predicted. In addition, treatment plans should be individualized according to the tumor's location, size, and clinical stage. This was supported by a review from a single institution, which showed that tumor stage, location, and size were significant prognostic factors in patients with vaginal cancer [33]. In addition, treatment should consider the following:

- Local anatomic constraints (e.g., removal of internal genitalia, supporting structures, rectosigmoid, lymphatics, and bladder) prevent wide negative surgical margins without an exenterative surgery.
- Psychosexual problems, including the patient's desire to obtain a functioning vagina.
- For most patients with **stage I tumors**, we recommend surgical excision. However, radiation therapy (RT) may be appropriate in some patients, especially for tumors >2 cm or lesions involving the mid to lower vagina.
- Radiotherapy is also used for tumors in the mid to lower vagina because of anatomic difficulties, as surgical resection of tumors at this site often requires vulvovaginectomy and inguinal node dissection to achieve negative margins and acceptable oncologic outcomes [34]. On the other hand, surgical resection is more appropriate for patients with lesions in the upper posterior vagina because the anatomy is preserved.
- We usually prefer RT to surgery because negative margins are difficult to achieve in tumors bigger than 2 to 3 cm in diameter [35]. Even if surgical resection is performed, obtaining an appropriate margin is challenging if the lesion is located close to the bladder or rectum.

If the tumor is located in the distal part of the vagina, the inguinal lymph nodes should also be examined.

Surgical: A radical hysterectomy, upper vaginectomy, and bilateral pelvic lymphadenectomy are required for the vaginal cancer approach. If hysterectomy has been performed previously, radical vaginectomy and bilateral lymphadenectomy should be performed to complete surgical treatment. When patients with stage I vaginal cancer are treated surgically, they appear to have the best results. This was supported by a literature review that showed that patients with early-stage disease had a median

five-year survival rate of 77%, much better than that of patients with late-stage disease, whether or not adjuvant RT was applied [6, 36].

Radiation therapy: For some patients, radiation alone is a sufficient treatment. For example, in a series of 91 women treated at a single institution, results obtained with modern RT for early-stage vaginal cancer were shown: In stage I patients (n = 38), the two-year overall survival rate, regional control rate, and distant metastasis-free survival rate were 96.2%, 80.6%, and 87.5%, respectively [20]. More than 2500 vaginal cancer patients were studied in the Surveillance, Epidemiology, and End Results (SEER) trial, which indicated that treatment with brachytherapy was better with 3.6 median survival years, rather than 6.1 years with external radiation alone [37].

A total radiation dose of at least 70 to 75 Gy is commonly suggested, with 45 to 50 Gy of external beam radiation and additional radiation provided via intracavitary or interstitial brachytherapy radiation, depending on the thickness of the primary tumor. Pelvic lymph nodes rimmed vaginal tumors, vaginal and paravaginal tissues, and inguinal lymph nodes should all be exposed to external radiation if the vaginal tumor is in the lower half of the vaginal canal. Brachytherapy radiation should be given immediately after the completion of external radiation. Vaginal tumors less than 5 mm thick can be treated using a vaginal roller or similar applicator, however tumors thicker than 5 mm require interstitial therapy for appropriate dosage and normal tissue preservation [38].

Surgery is usually not an option for patients with more advanced stages than II to IV. We frequently replace chemoradiotherapy for RT because of the relatively poor results of RT alone. However, given the lack of high-quality data on the benefits of chemoradiation, RT is a reasonable alternative, especially for patients who, for some reason, are not eligible for cisplatin-based chemotherapy.

Chemoradiation: In patients with advanced vaginal cancer, concurrent use of RT with chemotherapy (fluorouracil [FU] and/or cisplatin) is our preferred approach due to the usual issues associated with central tumor control. Because of the poor prognosis with radiation alone (predominantly local failures) [39], we often proceed to the combined use of radiation and concomitant chemotherapy in women with high-risk disease (e.g., stage III or IV or tumor size greater than 4) [40–42]. This is mainly based on extrapolating better results with chemoradiation for locally advanced cervical cancer treatment.

There are few data to support this approach, particularly in vaginal cancer, and these are mostly limited to small retrospective series [40, 42–44], which consistently show high rates of locoregional control after chemoradiotherapy and long-term radiation-related side effects. Compared to RT alone, it does not look worse. However, whether chemoradiation is beneficial for these patients or not is not entirely clear because of limited data:

- Most of these studies examined women with stage I disease or II, limiting their applicability to these patients.
- Because of the disease's rarity, no randomized clinical trials have been performed.

In a study of 71 patients, 20 patients who received definitive RT concomitant chemotherapy and 51 who did not receive chemotherapy were evaluated. It was found that 3-year and overall survival were statistically significantly longer in the

chemosensitive group, and disease-free survival rates were also longer in the chemotherapy group [45].

For patients with stage II to IV disease who are not considered candidates for chemoradiotherapy, RT (with intracavitary or interstitial therapy, depending on tumor thickness) is a reasonable alternative [39, 40, 46–49].

However, results after RT alone in advanced disease are not as good as in patients with stage I disease. In the same series from a single institution mentioned above, the two-year overall survival rate, regional control rate, and distant metastasis-free survival rate by stage were as follows [20]:

- Stage II – 92.3%, 64.7%, and 84.6%, respectively
- Stage III – 66.6%, 44.4%, and 50%
- Stage IV – 25%, 14.3% and 25%

In patients with advanced disease, surgery as a primary treatment modality is associated with poorer outcomes than chemoradiotherapy. For example, in a literature review, the mean five-year survival rates for patients with stage II, III, and IV disease after surgery were 52, 44, and 14%, respectively, with or without adjuvant radiotherapy [36].

In addition, negative margins in women with large or extensive lesions are usually challenging to achieve without sacrificing the bladder or rectum.

Neoadjuvant therapy: Radical surgery after neoadjuvant chemotherapy is a promising alternative to RT for these patients. However, we consider it mostly experimental until further data becomes available.

In a small prospective study of 11 patients with stage II disease who previously had three courses of 21 days of paclitaxel (175 mg/m²) and cisplatin (75 mg/m²) chemotherapy, the potential role of neoadjuvant therapy was demonstrated. 91% of these patients had a clinical response after neoadjuvant chemotherapy, and all were able to undergo surgical resection. The pathological complete response rate was 27% [50].

5. Complications

10–15% of patients with vaginal cancer will develop treatment-related complications [51]. These include rectovaginal or vesicovaginal fistulas, radiation cystitis or proctitis, rectal and vaginal strictures, and rarely vaginal necrosis. The proximity of the urethra, bladder, and rectum predisposes these structures to injury from surgery or radiation.

After radiation, women are advised to use a vaginal dilator to minimize the extent of vaginal stenosis. In general, we recommend that women start using the dilator one week after completing radiation and use it daily. Women who are sexually active regularly may need to use the dilator less frequently.

Women under 40 years of age who receive radiation for vaginal carcinoma are at higher risk for radiation-induced early menopause. In numerous ways, attempts to minimize the toxicity of radiation exposure by moving the ovaries to the back of the uterus or the lateral pelvic walls (oophoropexy) have been successful [52, 53]. It is recommended to perform oophoropexy in selected cases.

5.1 In case of recurrence

Recurrent patients may be candidates for surgery. However, for those who are not candidates for surgery for any reason, treatment options are rather limited because of the lack of prospective studies on this disease.

In patients with central recurrence and no other foci of disease, pelvic exenteration may be therapeutic with or without vaginal reconstruction [54–56]. Exenteration may also be considered in stage IVa patients, especially if a rectovaginal or vesicovaginal fistula is present.

Chemotherapy's role in recurrent or advanced vaginal cancer patients is unclear. Therefore, we administer chemotherapy to patients with recurrent vaginal cancer when there are no alternatives (e.g., surgery or radiotherapy [RT]) or when there is evidence of metastatic disease outside the pelvis. However, patients and providers should be aware that there is a lack of high-quality data to inform whether the benefits of treatment justify the toxicities associated with systemic chemotherapy. In the absence of clear benefits, these patients should be referred to palliative care when appropriate [57–60].

Cisplatin was recommended based on the experience of the Gynecological Oncology Group, which included 26 patients with advanced disease. Although the dose of cisplatin was sub-therapeutic by modern standards, these patients had insignificant activity (50 mg/m² every three weeks) [57]. Combination therapy with bleomycin, vincristine, mitomycin, and cisplatin also appears to be relatively ineffective in patients with advanced or recurrent disease, although it shows marked efficacy in early disease [58]. In patients with early-stage squamous vaginal carcinoma, anecdotal findings suggest an activity for carboplatin, a combination of vinblastine, bleomycin, and cisplatin, and irinotecan, as well as cisplatin [26, 59, 60]. However, a large series of these regimens is lacking to confirm activity in advanced disease.

6. Post treatment follow-up

The optimal surveillance strategy has not yet been determined, and clinical practice varies. We agree with the recommendations of the Society of Gynecological Oncology (SGO) [61]:

- Review of symptoms and physical examination:
- For low-risk disease (early stage, treated surgically only, no adjuvant therapy) - Every six months for the first two years and annually after that.
- For high-risk disease (advanced stage, treated with primary chemo/radiotherapy or surgery plus adjuvant therapy) - Every three months for the first two years, every six months for years 3 through 5, and annually after that.
- Cervical cytology (or vaginal cytology if the cervix has been removed) annually. However, the evaluations concluded that there is insufficient evidence to support the use of cytology to detect cancer recurrence but that it may help detect other neoplasms of the lower genital tract.

- Routine use of imaging studies is not recommended. Computed tomography (CT) and/or positron emission tomography (PET) should be performed if recurrence is suspected.
- If abnormalities are discovered during a physical examination, a vaginal colposcopy and biopsy are indicated.

Given the risk of multifocal vaginal illness and other human papillomavirus (HPV)-related diseases like cervical, vulvar, and anal neoplasia, these patients should also be screened for these diseases.

Following the therapy, sexual dysfunction and body image changes are prevalent and should be addressed during follow-up visits [62, 63].

7. Prognosis

The stage at presentation, which reflects the extent and depth of tumor penetration, is the most critical variable impacting the prognosis [13, 46, 49, 64–67]. Data from the United States National Cancer Database, for example, have shown an increased risk of death in women with stage II or higher disease and/or vaginal cancer with tumor size >4 cm (five-year survival 65% vs. 84 percent for tumors ≤ 4 cm), and the mortality rate for women with melanoma was 51% higher than for squamous cell carcinoma [67]. The lower survival rates in women with vaginal cancer compared with those with cervical or vulvar cancer may reflect the high rate of vaginal tumors diagnosed at an advanced stage and the potential for treatment complications that preclude aggressive treatment.

8. Conclusion

The stage at presentation, which indicates the degree and depth of tumor penetration, is the most critical variable impacting the prognosis in primary vaginal squamous cell cancer. The lower survival rates in women with primary vaginal cancer than those with cervical or vulvar cancer are related to a high diagnosis rate of advanced-stage vaginal tumors at baseline and potential treatment complications that preclude aggressive treatment.

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Conflict of interest

The authors declare no conflict of interest.

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