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International Journal of Gynecology and Obstetrics

FIGO CANCER REPORT 2012

Cancer of the vagina

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1. Staging

A description of the staging classification for primary vaginal carcinoma is detailed in Table 1.

Table 1
Cancer of the vagina.

FIGO Stage	Description
I	The carcinoma is limited to the vaginal wall
II	The carcinoma has involved the sub-vaginal tissue but has not extended to the pelvic wall
III	The carcinoma has extended to the pelvic wall
IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to Stage IV
IVA	Tumor invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

1.1. Anatomy

1.1.1. Primary site

The vagina extends from the vulva upward to the uterine cervix. Cases should be classified as carcinoma of the vagina when the primary site of the growth is in the vagina. Tumors present in the vagina as secondary growths from either genital or extra-genital sites should be excluded. A growth that has extended to the portio of the cervix and reached the area of the external os should always be allotted to carcinoma of the cervix. A growth limited to the urethra should be classified as carcinoma of the urethra. A tumor involving the vulva should be classified as carcinoma of the vulva. There should be histologic verification of the disease.

1.1.2. Nodal stations

The upper two-thirds of the vagina is drained by lymphatics to the pelvic nodes, with the lymphatics paralleling the course of the uterine artery and the vaginal artery to the obturator, hypogastric (internal iliac), and external iliac nodes. The distal third of the vagina drains to the inguinal-femoral nodes. Some lesions, particularly those involving the posterior vaginal wall, may drain via pararectal lymphatic channels to presacral nodes.

1.1.3. Metastatic sites

The most common sites of distant spread include the lungs, liver, and bony skeleton. The rules for staging are similar to those for carcinoma of the cervix.

1.1.4. Histopathologic types

Squamous cell carcinoma is the most common type of cancer occurring in the vagina. Infrequently an adenocarcinoma may occur.

1.1.5. Histopathologic grades (G)

- GX: Grade cannot be assessed.
- G1: Well differentiated.
- G2: Moderately differentiated.
- G3: Poorly or undifferentiated.

2. Introduction

Carcinoma of the vagina constitutes only about 2% of malignant neoplasms of the female genital tract [1]. The vagina, however, can be a common site of metastatic gynecological cancer, by either direct extension of cervical or vulvar tumors, or through lymphatic or vascular deposits, as seen in endometrial cancer and gestational trophoblastic disease, respectively. Metastatic or direct extension of non-gynecologic tumors to the vagina can also occur from the urinary bladder, urethra, periurethral glands, rectum, and rarely the breast, lung, or other sites.

Up to 30% of patients with primary vaginal carcinoma have a history of in situ or invasive cervical cancer treated at least 5 years earlier [2–4]. (It is arbitrarily assumed that an invasive squamous cell carcinoma occurring in the vagina more than 5 years after an invasive squamous cell carcinoma of the cervix is a new primary cancer.) Some vaginal cancers are preceded by vaginal intraepithelial neoplasia (VAIN), although the true malignant potential of VAIN is not known [5,6]. Prior pelvic radiation has also been considered a possible cause of vaginal cancer [7,8].

Most vaginal cancers occur in postmenopausal or elderly women [1]. When occurring in younger patients, the disease seems to be etiologically related to cervical neoplasia, and thus human papillomavirus (HPV) dependent [9]. Histologically, approximately 90% of primary vaginal cancers are squamous cell lesions.

3. Screening

Routine screening for vaginal cancer following hysterectomy for benign disease is not recommended because these women are at extremely low risk of developing vaginal cancer. Women with a history of cervical intraepithelial or invasive neoplasia are at increased risk, but regular cytologic screening gives a low yield. The incorporation of newer testing modalities, including HPV testing, may allow the screening interval to be increased, and cost-effective screening, in this group of patients [10].

4. Vaginal intraepithelial neoplasia (VAIN)

For patients with an abnormal pap smear and no gross abnormality, vaginal colposcopy and use of Lugol's iodine to stain the vagina are necessary. Biopsy of colposcopically abnormal areas is necessary, usually under anesthesia. Excisional biopsy is useful for lesions involving the vaginal vault, where occult carcinoma may be found in up to 28% of patients with VAIN [11].

Treatment of VAIN must be individualized. Numerous treatments, ranging from local surgical excision or ablation through to intracavitary radiotherapy, have been used. Selection of the appropriate treatment is usually based on a careful study of several factors, including the general medical condition of the patient, the histology of the lesion, the location and extent of the disease, as well as the experience and expertise of the treating medical team. The proximity of the urethra, bladder, and rectum to the vaginal epithelium is an important factor to be considered. Damage or injury to these structures can occur with possible fistula formation, particularly when the patient has had prior pelvic radiation therapy.

Laser vaporization with a carbon dioxide laser is an effective treatment for VAIN [12]. This technique generally requires local or general anesthesia.

The use of topical 5-fluorouracil (5-FU) is a relatively simple ambulatory treatment, which does not require anesthesia or complicated equipment [13]. This approach may be especially valuable for patients with widespread or multifocal disease, which would require an extensive surgical procedure. Side effects are usually minimal, as long as it is not used more than twice a week.

Imiquimod 5% cream might represent an alternative method of management in young, HPV-positive women with multifocal high-grade lesions (VAIN 2/3) [14].

Excisional procedures, either with electrosurgical loops or a scalpel excision, have also been used to treat VAIN. Surgical excision is particularly appropriate for vault lesions [15]. Total vaginectomy and split-thickness skin grafting may be occasionally necessary to treat extensive lesions that involve virtually the entire length of the vaginal tube and where other conservative methods have been unsuccessful. **Level of Evidence C**

5. Invasive carcinoma

Most patients present with painless vaginal bleeding and discharge, and definitive diagnosis can usually be made by biopsy of a gross lesion detected on speculum examination. This can often be done in the office, but may be facilitated by examination under anesthesia.

5.1. Treatment

Whenever possible, patients should be referred to tertiary referral units because of the rarity of these lesions and the limited experience of most practitioners with the specialized techniques used to treat these cancers effectively. All treatment must be individualized, and will vary depending on the stage of disease and the site of vaginal involvement. For most patients, it is important to try to maintain a functional vagina.

5.1.1. Surgery

Surgery has a limited role because of the close proximity of the bladder and rectum, but may be useful in the following situations [1,16,17]:

1. In patients with Stage I disease involving the upper posterior vagina: If the uterus is still in situ, radical hysterectomy, upper vaginectomy to achieve clearance of at least 1 cm, and pelvic lymphadenectomy may be performed. If hysterectomy has been performed previously, radical upper vaginectomy and pelvic lymphadenectomy may be appropriate.

2. In young patients who require radiation therapy: Pretreatment laparotomy or laparoscopy may allow ovarian transposition, or in selected cases, surgical staging and resection of any bulky positive lymph nodes.

3. In patients with Stage IVA disease, particularly if a rectovaginal or vesicovaginal fistula is present: Primary pelvic exenteration may be a suitable treatment option for selected patients, either combined with pelvic lymphadenectomy or preoperative radiation [2]. Bilateral groin dissection should be considered in such patients if the lower third of the vagina is involved.

4. In patients with a central recurrence after radiation therapy: Surgery will usually necessitate some type of pelvic exenteration in such patients. **Level of Evidence C**

5.1.2. Radiation therapy

Radiation therapy is the treatment of choice for most patients with vaginal cancer, and usually requires careful integration of teletherapy and intracavitary or interstitial brachytherapy. External beam and brachytherapy techniques may vary widely, depending on the precise location of the tumor and its relationship to critical structures.

Although some authors have advocated treatment with brachytherapy alone for small Stage I (or even Stage II) cancers [18–21], a combination of external beam irradiation and brachytherapy probably reduces the risk of local–regional recurrence in such cases. For larger lesions, treatment is started with approximately 45–50 Gy external radiation to reduce the primary tumor volume and to treat the pelvic nodes. This is then supplemented with brachytherapy or external beam boosts to gross disease in the primary site and involved lymph nodes.

There is evidence for improved local control when the dose to the primary tumor exceeds 70 Gy [19,21]. This is most easily achieved using brachytherapy if the entire tumor volume can be treated to the necessary dose without exceeding normal tissue tolerance. Although brachytherapy is preferred whenever possible, highly conformal external beam boosts may achieve more homogeneous coverage of tumor in selected patients who have massive tumors, or intimate association of tumor with critical structures, for example the rectovaginal septum.

If the distal one-third of the vagina is involved, the groin nodes should be treated or dissected. **Level of Evidence C**

There is limited reported experience with chemoradiation for vaginal cancer [20–22]. However, extrapolating from the favorable results reported for cervical cancers, the concurrent use of cisplatin-based chemoradiation may be appropriate, particularly in locally advanced cases. **Level of Evidence D**

5.2. Prognosis

Although the reported overall 5-year survival for vaginal cancer is only about 52% [1], recent reports have indicated 5-year survival rates comparable to cervical cancer [18–20]. A study of 193 patients from the M.D. Anderson Cancer Center in Houston reported 5-year disease-specific survival rates of 85% for 50 patients with Stage I disease, 78% for 97 patients with Stage II, and 58% for 46 patients with Stages III–IVA [22].

6. Special situation

6.1. Adenocarcinoma

Approximately 10% of primary vaginal carcinomas are adenocarcinomas, and they may arise in areas of vaginal adenosis in diethylstilbestrol (DES) exposed patients, in Wolffian rest elements, periurethral glands, or foci of endometriosis. DES-related clear cell carcinomas of the vagina occurred mainly in young women, but as the DES-exposed cohort is now over 50 years of age, DES-related tumors are now rare. In a series of 26 patients with non-DES-related

vaginal adenocarcinomas reported from the M.D. Anderson Cancer Center in 2007, the median age was 54 years [23].

6.1.1. Treatment

In general, adenocarcinomas are treated in a similar manner to squamous lesions, although greater emphasis should be placed on combined modality therapy, even for small tumors, because of the greater propensity for local recurrence [23].

6.1.2. Prognosis

Prognosis for DES-related clear cell carcinomas of the vagina is generally good, with an overall survival of 78% [24]. Survival for non-DES-related adenocarcinomas is significantly worse than for squamous cancers. A recent study of 26 such patients from the M.D. Anderson Cancer Center reported an overall 5-year survival of only 34%, with a higher rate of both local recurrences and distant metastases [23].

6.2. Vaginal melanoma

Malignant melanomas of the vagina are rare, and almost all cases occur in white women [25]. They most commonly occur in the distal vagina, particularly on the anterior vaginal wall [25,26].

Most are deeply invasive and radical surgery has been the mainstay of treatment, often involving some type of pelvic exenteration. Recently, more conservative local excisions have been used, with comparable survival rates reported [25–27]. This is usually combined with postoperative radiation. Overall 5-year survival is about 10%. **Level of Evidence C**

6.3. Sarcoma botryoides

Sarcoma botryoides is a highly malignant tumor of the rhabdomyoblasts. These neoplasms are found in infants and children and usually present with discharge, bleeding or a visible mass at the introitus.

In the past, exenterative surgery was used for these lesions, but survival was poor. More recently, conservative surgery has been used in conjunction with preoperative or postoperative chemotherapy and radiotherapy with significantly improved survival. Most reported chemotherapeutic experience has been with vincristine, actinomycin D, and cyclophosphamide (VAC) [28–30].

If the lesion is small and can be resected with organ preservation, surgery should be the initial approach. For bulkier lesions, preoperative chemotherapy or localized teletherapy or brachytherapy may be used.

Extended radiotherapy fields are not recommended, as they may produce significant developmental problems with the bony pelvis by destroying or interfering with growth centers in these structures.

Conflict of interest

The authors declare that they have no conflicts of interest.

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