

EVERYONE'S GUIDE FOR CANCER THERAPY
Malin Dollinger, MD, Ernest H. Rosenbaum, MD,
Margaret Tempero, MD, and Sean Mulvihill, MD
4th Edition, 2001

Vulva

Jeffrey L. Stern, M.D.

Malignant tumors of the vulva account for 3 to 5 percent of all cancers of the female genital tract and are easily cured when diagnosed at an early stage. Generally, because of better access to routine gynecologic care, these cancers are being diagnosed at an earlier stage.

Surgery has long been the mainstay of treatment, but views about the extent of surgery have changed over the years. In the 1940s, it was noted that the failure rate was much higher with conservative surgical measures. Since then, more radical operations have been performed with a marked improvement in the survival rate. But recently, as younger women with earlier disease are diagnosed with vulvar cancer, there has been a trend toward more conservative surgery with a greater emphasis on limiting the psychosexual consequences of therapy and preserving the normal female genital anatomy. Similarly, there has been a recent trend toward using local radiation therapy with chemotherapy in advanced cases either to reduce the amount of surgery needed or to improve the chance that the tumor can be removed.

Types Squamous cell carcinomas account for about 86 percent of all vulvar malignancies. Melanoma accounts for another 6 percent, adenocarcinoma of the Bartholin's gland for 4 percent,

sarcomas for 2 percent, basal cell carcinoma for 2 percent and Paget's disease for 0.5 percent of all vulvar cancers.

Some physicians believe that the grade of the tumor cells as seen under the microscope is also significant. Immature, or undifferentiated, cells are more virulent and aggressive. Grade I (mature, or well-differentiated) cancers have a better prognosis than grade 3 (poorly-differentiated) tumors.

How It Spreads Squamous cell carcinoma arises in the skin of the genitalia and stays confined to the skin for an estimated 1 to 10 years. (At this stage, it is referred to as a carcinoma in situ, vulvar intraepithelial neoplasia-VIN, or vulvar squamous intraepithelial lesion-SIL). Eventually, it becomes invasive. With time it becomes locally destructive, growing to involve the urethra, vagina and the anus. It can also spread through the lymphatic system to the lymph nodes in the groin, then to the lymph nodes in the pelvis. Distant metastases, most frequently to the lungs and liver, are relatively rare (*see "Cervix"*).

What Causes It Like carcinoma of the cervix, the risk factors for the development of vulvar cancer are primarily related to the likelihood of exposure to the sexually transmitted human papilloma virus (HPV).

RISK FACTORS

- The vast majority of women with invasive vulvar carcinoma are postmenopausal. But there has been a definite trend over the past two decades of an increasing incidence of carcinoma in situ and cancer in younger women. Forty percent of women with carcinoma in situ are under 40 years of age.
- Five to ten percent of women with invasive vulvar carcinoma have a history of genital warts, and 15 percent have a history of, or subsequent diagnosis of preinvasive (carcinoma in situ) or invasive carcinoma of the cervix.
- Over 90 percent of the invasive squamous lesions of the vulva are associated with human papilloma virus types 16 or 18.
- Other sexually transmitted diseases such as syphilis, lymphogranuloma venereum and herpes simplex virus II also increase the risk for vulvar carcinoma.
- There is a higher incidence in women from lower socioeconomic groups, women with multiple partners and women with a history of infectious vulvitis or a history of vulvar dystrophy (abnormal benign or premalignant skin changes).

SCREENING

Careful visual and manual inspection of the external genitalia during an annual gynecologic examination is important. Women with a diagnosis of an HPV-related infection of any portion of the lower genital tract should undergo a careful colposcopic (magnification) examination of the entire lower genital tract.

COMMON SIGNS AND SYMPTOMS

The most common signs and symptoms are a lump or an ulcer, itching, pain, burning, bleeding and discharge. Unfortunately, many women do not get medical attention when these signs appear. At the time of the diagnosis, two out of three women with vulva carcinoma have had symptoms for the more than six months and one out of three has had symptoms for more than a year.

DIAGNOSIS

Physical Examination

- Careful visual and manual inspection of the external genitalia, anus and groin lymph nodes is crucial.
- Because of the association with precancerous and cancerous lesions of the cervix and vagina, a careful pelvic examination is also necessary.
- The majority of squamous cell carcinomas arise in the labia majora and minora and are frequently associated with vulvar dystrophy. The clitoris, outer vagina and the skin between the vagina and anus (perineum) may also be involved.

Endoscopy and Biopsy

- The definitive diagnosis is made on a biopsy, sometimes under colposcopic direction (magnification) for smaller lesions.
- Upon diagnosis, a metastatic work-up is done, including a chest x-ray, a complete blood count and serum and liver function tests, and CT scan of the pelvis and abdomen.

Cystoscopy and proctoscopy may also be recommended for advanced cancer. A serum CEA and squamous cell antigen may be elevated in some women.

STAGING

Staging is based on physical findings and x-ray results. Both the FIGO (Federation of International Gynecologists and Obstetricians) and the TNM classifications are used to stage vulvar cancer.

TREATMENT OVERVIEW

The prognosis for vulvar cancer depends on several factors-cell type, stage (which emphasizes local tumor extent), the presence or absence of groin node metastases, the size of the lesion, the depth of invasion, whether blood or lymphatic vessels are involved, and the grade of the tumor and the pattern of invasion.

At diagnosis, about 35 percent of all vulvar carcinoma are Stage I, 30 percent of women have Stage II, 25 percent have Stage III and 10 percent have Stage IV disease. The overall five-year survival rate for all women with invasive squamous cell carcinoma of the vulva is 69 percent.

Surgery The standard therapy for the past four decades has been radical surgical excision of the vulva and the removal of the lymph nodes in the groin and, occasionally, the pelvis. External beam radiation therapy is frequently given to the groin and pelvis after surgery to women with positive groin and/or pelvic lymph nodes on one or both sides.

Over the past 15 years, less radical surgery and the removal of the groin nodes on one side has been shown to be equally effective in small, early-stage disease. Despite this trend toward conservative therapy, experience has taught that limiting surgery because of advanced age or frailty can result in overwhelming problems with locally advanced recurrent cancer in women who live longer than expected.

A radical vulvectomy and groin dissection is extraordinarily well tolerated and can be done in phases if the patient's medical condition warrants. Sexual function is also surprisingly more satisfactory than one would think and can depend on the extent of surgery and the use of radiation therapy.

Complications of radical surgery for vulvar cancer include wound breakdown or infection, chronic leg swelling, collection of lymphatic fluid in the groin (lymphocyst), scarring of the vaginal opening, vaginal or uterine prolapse, loss of urine when coughing (stress incontinence), blood clots in the leg that can dislodge and go to the lung (pulmonary embolism, approximately 1 to 3 percent of women), and death (approximately 1 to 2 percent).

Chemotherapy and Radiotherapy In recent years, chemotherapy has been used in combination with local external beam radiation therapy and occasionally with interstitial radiation, in which radioactive material is temporarily placed directly into the cancer. This treatment has been used for women with advanced cancers, allowing the subsequent surgical removal of the tumor or the preservation of the bladder or anus.

Currently, there is no standard chemotherapy for advanced or recurrent cancer, but drugs that are sometimes effective for other squamous cell carcinomas of the genital tract-such as cisplatin, mitomycin-C, 5-fluorouracil (5-FU), carboplatin and ifosfamide, Cytosan and bleomycin-have been used with some success.

TREATMENT BY STAGE

STAGE 0

TNM Tis, NO MO

Vulvar carcinoma in situ, also known as intraepithelial neoplasia or high-grade SIL.

Standard Treatment Standard therapy has been either wide local excision or laser vaporization. Occasionally a partial or total vulvectomy is performed with or without skin grafting.

Five-Year Survival 100 percent.

Investigational None.

STAGE IA

TNM T1, N0, M0

The tumor is confined to the vulva or perineum, is less than 2 cm in diameter, and there is less than 1 mm invasion.

STAGE IB

TNM T1, N0, M0

The tumor is confined to the vulva or perineum, is less than 3/4 in. (2 cm) in diameter and there is stroma invasion greater than 1 mm. There are no nodal metastases.

Standard Treatment For lesions with less than 1 mm of invasion and no vascular involvement, a wide local excision is adequate therapy.

For lesions with deeper invasion that are clearly on one side of the vulva, a radical local excision (partial radical vulvectomy) with a complete groin node dissection on the same side is performed.

For other Stage I cancers involving the skin between the vaginal opening and the anus or clitoris, a radical vulvectomy and groin lymph node dissection on both sides are performed.

Five-Year Survival Over 90 percent.

Investigational

- Conservative surgery.
- Treatment with radiation therapy with or without chemotherapy (5-FU + cisplatin).

- Treatment with chemotherapy for high risk factors: positive groin nodes, microscopic vessel involvement.

STAGE II

TNM T2, N0, M0

The tumor is confined to the vulva and/or perineum and is more than 3/4 in. (2 cm) in diameter but has not spread to lymph nodes.

Standard Treatment Radical vulvectomy with removal of the groin lymph nodes, usually on both sides.

Five-Year Survival 80 percent, up to 90 percent for those patients with surgically negative groin nodes.

Investigational Same as Stage I.

STAGE III

TNM T3 or less, N1 or less, M0

The tumor may be of any size with either adjacent spread to the vagina, urethra or anus or metastases to the groin lymph nodes on one side.

Standard Treatment Radical vulvectomy with groin lymph node dissection on both sides is the standard therapy. Sometimes, a pelvic lymph node dissection is done at the time of surgery if the groin lymph nodes are positive.

External beam radiation therapy is frequently given postoperatively to the groin and pelvis if there are groin lymph node metastases. With two or more pathologically positive groin nodes, there has been a significantly better survival rate with pelvic radiation than with pelvic lymph node dissection in a study conducted by the Gynecologic Oncology Group.

Women with large vulvar lesions who have only a small margin of normal tissue around the tumor on microscopic examination of the surgical specimen may be treated with postoperative external beam radiation therapy to the remaining genital skin.

Five-Year Survival About 50 percent.

Investigational

- Radiation therapy has been used to improve resectability and to decrease the amount of surgery necessary in women with large cancers or cancers involving the urethra or anus.
- Preoperative external beam and interstitial radiation therapy (radioactive substances inserted directly into the tumor for one to two days) with or without chemotherapy (cisplatin, 5-FU + cisplatin, cisplatin + ifosfamide).

- Treatment with cisplatin + 5-FU for high risk factors: positive groin nodes, microscopic vessel involvement, close margins, large tumors.

STAGE IVA

TNM Any tumor T, N2, M0, or T4, N0, M0

The tumor may involve the upper urethra, the bladder mucosa, the rectal mucosa, the pelvic bone, and/or there are bilateral groin node metastases.

Standard Treatment Options include:

- Radical vulvectomy, removal of the lymph nodes on both sides and removal of the vagina, bladder and/or rectum (pelvic exenteration).
- Surgery followed by radiation therapy in those with close surgical margins.
- Radiation therapy with combination chemotherapy (5-FU + cisplatin, 5-FU + mitomycin-C + cisplatin, cisplatin + ifosfamide or cisplatin alone) occasionally followed by radical surgery.

Five-Year Survival About 15 percent.

Investigational

- External beam radiation therapy and interstitial radiation therapy with or without various doses and kinds of chemotherapeutic drugs are being evaluated.

STAGE IVB

TNM Any T, any N, M1a, or M1b.

There are distant metastases including pelvic lymph nodes.

Standard Treatment Vulvar cancer that has spread to distant sites is treated with chemotherapy, but there is no standard chemotherapeutic regimen. Cisplatin, carboplatin, ifosfamide, methotrexate, vincristine and bleomycin are all commonly used drugs.

Usually palliative local surgical removal or radiation therapy to the vulva is done for local symptom relief.

Women with metastases to the pelvic nodes are treated with pelvic external beam radiation therapy.

Five-Year Survival From 5 percent (metastases to the lungs or liver) to 25 percent (metastases to the pelvic lymph nodes).

Investigational

- Ifosfamide, carboplatin, 5-FU, mitomycin-C, methotrexate, vincristine, bleomycin, Taxol, Topotecan, and cisplatin in various combinations and doses are being investigated.

RECURRENT CANCER

Recurrences are more common in women with large lesions or with positive nodes. They usually occur within the first three years after treatment. The recurrence may be anywhere on the remaining external genitalia (10%), in the groin or pelvic nodes, or at distant sites. Symptoms of recurrent cancer may include bleeding, pain in the genitals, groin, pelvis or legs, leg swelling (edema), weight loss, chronic cough and chest pain.

Treatment options include wide local excision (for a local recurrence), radical local excision, pelvic exenteration (removal of vulva, vagina, bladder, rectum) external beam radiation therapy, interstitial radiation therapy and chemotherapy.

TREATMENT FOLLOW-UP

After therapy, most women are followed at three month intervals with a careful physical examination, x-ray studies if symptoms warrant, and with a serum CEA or squamous cell carcinoma antigen if elevated prior to treatment.

TREATING OTHER VULVA MALIGNANCIES

MALIGNANT MELANOMA OF THE VULVA

Although relatively rare, this is the second most common type of vulvar cancer. It occurs most commonly in women around the age of menopause and in postmenopausal women.

More than 80 percent of melanomas arise from the labia minora and clitoris. Most women seek medical attention because of itching, bleeding or a lump. Superficially

spreading melanomas and mucocutaneous melanomas account for approximately 60 percent and 10 percent respectively of all vulvar melanomas and are somewhat slow growing until invasion occurs. Thirty percent are nodular melanomas, which behave much more aggressively.

Standard Treatment Radical vulvectomy and bilateral groin node dissection is the standard therapy, although over the past few years there has been a trend toward more conservative surgery.

Melanomas that are less than 0.7 mm in thickness without vascular space involvement can be treated by a wide local excision with a 3/4 in. (2 cm) skin margin, without a groin dissection.

The role of a pelvic lymph node dissection has not been determined, but if the groin nodes are involved, a pelvic lymph node dissection may be performed. The prognosis and survival is determined in large part by the depth of invasion and whether there are metastases.

Five-Year Survival 40 to 80 percent depending on the stage and depth of invasion.

BASAL CELL CARCINOMA

This type of vulvar cancer invades adjacent tissues but rarely metastasizes. It has an excellent cure rate and is managed with only a wide local excision.

ADENOCARCINOMA OF THE VULVA

This is a rare tumor and generally arises from the Bartholin's gland, located at the opening of the vagina. Survival is related to stage. Treatment is usually radical vulvectomy and bilateral groin node dissection.

PAGET'S DISEASE

This occurs most commonly in postmenopausal white women. Intense itching is the most common symptom.

About 30 percent of cases of Paget's disease are associated with an underlying invasive adenocarcinoma, and for these the prognosis is quite poor. But Paget's disease confined to the vulvar skin (stage 0) has an excellent prognosis with only rare instances of subsequent invasion or death.

If there is no underlying adenocarcinoma, a wide local excision or total vulvectomy is all that is required.

If there is an underlying adenocarcinoma, a radical vulvectomy and bilateral groin dissection is usually performed.

VULVAR SARCOMAS

These account for only 1 to 2 percent of all vulvar malignancies. The majority of vulvar sarcomas arise from the smooth muscle and are known as leiomyosarcomas.

Treatment is usually radical surgery sometimes followed by radiation therapy.

THE MOST IMPORTANT QUESTIONS YOU CAN ASK

- What type of cancer do I have?
- Is a radical vulvectomy and removal of the groin lymph nodes on both sides necessary if I have Stage I disease?
- Is there a role for radiation therapy with or without chemotherapy for my cancer?
- What is my prognosis?
- What qualifications do you have for treating cancer? Will a gynecologic oncologist be involved in my care?