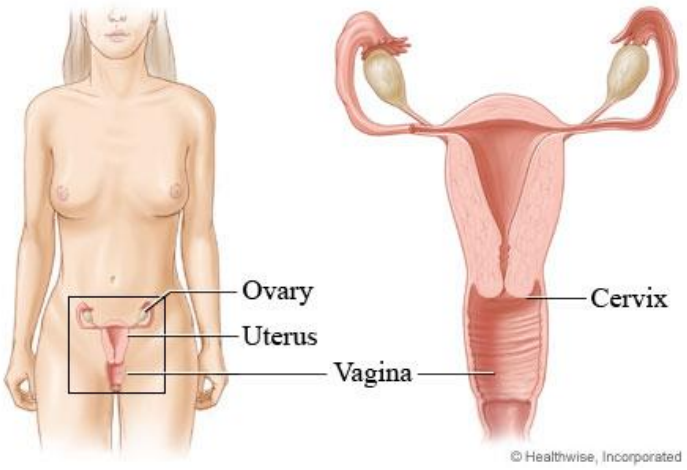
Cancer Association of South Africa (CANSA)

Fact Sheet
on
Cancer of the Vagina

Introduction

The vagina is a fibromuscular tubular tract, a sex organ, and has two main functions - sexual intercourse and childbirth. In humans, this passage leads from the opening of the vulva to the uterus (womb), but the vaginal tract ends at the cervix. Unlike men, who have only one genital orifice, women have two, the urethra and the vagina.

The vaginal opening is much larger than the urethral opening, and both openings are protected by the labia.



[Picture Credit: Female Reproductive System]

Kaltenecker, B. & AlEssa, A.M. 2020.

"Primary vaginal cancer is rare, making up 1% to 2% of all female reproductive tract cancers. The vagina is a unique organ with distinct tissue types and planes. It is a 7 to 10 cm long fibromuscular tube extending from the cervix to the vulva. It sits posterior to the urethra and bladder and anterior to the rectum. The organ is divided into three parts, which are important for classifying tumor location and lymphatic drainage. The lower third is below the level of the bladder base with the urethra anteriorly. The middle third is adjacent to the bladder base, and the upper third is at the level of the vaginal fornices. The vaginal fornices are denoted as anterior, posterior, and lateral with respect to the cervix. However, the borders of the vagina are surrounded by similar histologic cell types from the cervix and vulva. Many diseases that occur in the vulva or cervix can also occur in the vagina. Vaginal cancer is an uncommon gynecologic malignancy. Diagnosis of primary vaginal cancer is rare because most of these lesions (approximately 80% to 90%) will be metastatic from another primary site. The majority of these metastases arise from other reproductive organs such as the cervix, endometrium, or ovary, although they can also metastasize from distant sites such as the

colon, breast, and pancreas. Once there is a suspicion of primary vaginal cancer, this should be confirmed histologically with biopsy."

Kombathula, S.H., Rapole, P.S., Prem, S.S. & Badhe, B. 2019.
"Small cell carcinoma (SmCC) of the vagina is a rare and aggressive tumour. It comprises only 1% -2% of all gynaecological malignancies 85% of the patients with SmCC vagina die within a year of diagnosis."

Staples, J.N. & Duska, L.R. 2019.
"The Pap smear is the only proven screening intervention in the field of gynecologic oncology. Women should receive treatment for precancerous conditions of the cervix, vulva, vagina, and endometrial lining. Women with inherited conditions should consider having a risk-reducing surgery once they have finished childbearing. The human papilloma virus vaccination should be offered to all girls and boys aged 11 to 12 years, and can also be given as early as age 9 and through 26 years of age."

Tumour Grade and Tumour Stage
Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope.

Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

<u>What are the cancer stages?</u>
Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.
- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

<u>TNM staging</u>
Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is

staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical "grade" to most cancers.

Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.

The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)
- G4: Undifferentiated (high grade)

Incidence of Cancer of the Vagina in South Africa

According to the outdated National Cancer Registry (2017), known for under reporting, the following number of cancer of the vagina cases was histologically diagnosed in South Africa during 2017. 'Histologically diagnosed' refers to cases where a biopsy (small sample of tissue) was submitted to a pathological laboratory where a pathologist confirmed a cancer diagnosis:

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	200	1:1 274	0,48%
Asian females	5	1:2 660	0,39%
Black females	151	1:1 258	0,81%
Coloured females	14	1:1 619	0,31%
White females	30	1:1 123	0,17%

The frequency of histologically diagnosed cases of cancer of the vagina in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	2	6	32	45	47	38	22	8
Asian females	0	0	0	1	1	1	2	0
Black females	2	5	28	37	35	26	11	7
Coloured females	0	1	1	3	4	4	1	0
White females	0	0	3	4	7	7	8	1

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

According to **Bruni, *et al*.,** (2019), the burden of cervical cancer for South Africa for 2018 is estimated as:

- Annual number of vaginal cancer cases 108
- Annual number of vaginal cancer deaths 33

Cancer of the Vagina

Secondary cancers in the vagina are more common than primary vaginal cancer, and usually come from the neck of the womb (cervix), the lining of the womb (endometrium) or from nearby organs such as the bladder or bowel.

There are several types of vaginal cancer:

Squamous cell carcinoma

About 70 of every 100 cases of vaginal cancer are *squamous cell carcinomas***.** These cancers begin in the squamous cells that make up the epithelial lining of the vagina. These cancers are more common in the upper area of the vagina near the cervix.

Adenocarcinoma

Cancer that begins in gland cells is called *adenocarcinoma*. About 15 of every 100 cases of vaginal cancer are adenocarcinomas. The usual type of vaginal adenocarcinoma typically develops in women older than 50. One certain type, called *clear cell adenocarcinoma*, occurs more often in young women who were exposed to diethylstilbestrol (DES) in utero (when they were in their mother's womb).

Melanoma

Melanomas develop from pigment-producing cells that give skin its colour. These cancers usually are found on sun-exposed areas of the skin but can form on the vagina or other internal organs. About 9 of every 100 cases of vaginal cancer are melanomas.

Sarcoma

A sarcoma is a cancer that begins in the cells of bones, muscles or connective tissue. Up to 4 of every 100 cases of vaginal cancer are sarcomas. These cancers form deep in the wall of the vagina - not on its surface. There are several types of vaginal sarcomas. *Rhabdomyosarcoma* is the most common type of vaginal sarcoma. It is most often found in children and is rare in adults. A sarcoma called *leiomyosarcoma* is seen more often in adults. It tends to occur in women older than 50.

Other cancers

Cancers of the vagina are much less common than cancers that start in other organs (such as the cervix, uterus, rectum or bladder) and then spread to the vagina. These cancers are named after the place where they started.

Senkomago, V., Henley, S.J., Thomas, C.C., Mix, J.M., Markowitz, L.E. & Saraiya, M. 2019.

"Human papillomavirus (HPV) causes nearly all cervical cancers and some cancers of the vagina, vulva, penis, anus, and oropharynx (1).* Most HPV infections are asymptomatic and clear spontaneously within 1 to 2 years; however, persistent infection with oncogenic HPV types can lead to development of precancer or cancer (2). In the United States, the 9-valent HPV vaccine (9vHPV) is available to protect against oncogenic HPV types 16, 18, 31, 33, 45, 52, and 58 as well as nononcogenic types 6 and 11 that cause genital warts. CDC analyzed data from the U.S. Cancer Statistics (USCS)† to assess the incidence of HPV-associated cancers and to estimate the annual number of cancers caused by HPV, overall and by state, during 2012-2016 (3,4). An average of 43,999 HPV-associated cancers were reported annually, and an estimated 34,800 (79%) of those cancers were attributable to HPV. Of these 34,800 cancers, an estimated 32,100 (92%) were attributable to the types targeted by 9vHPV, with 19,000 occurring among females and 13,100 among males. The most common were cervical (9,700) and oropharyngeal cancers (12,600). The number of cancers estimated to be attributable to the types targeted by 9vHPV ranged by state from 40 to 3,270 per year. HPV vaccination is an important strategy that could prevent these cancers, but during 2018, only half of adolescents were up to date on HPV vaccination (5). These surveillance data from population-based cancer registries can be used to inform the planning for, and monitor the long-term impact of, HPV vaccination and cancer screening efforts nationally and within states."

Adams, T.S. & Cuello, M.A. 2018.

"Diagnosis of a primary vaginal cancer is rare because most of these lesions will be metastatic from another primary site. Although cancer of the vagina is more common in postmenopausal women, an increase in young women being diagnosed with primary vaginal cancer has been reported, especially in countries with a high HIV prevalence. This will be associated with persistence of high-risk HPV infection. The emphasis should be on primary prevention with prophylactic HPV vaccination. Once there is a suspicion of a primary vaginal cancer, this should be confirmed histologically with biopsy. Staging has been done clinically, similar to cervical cancer; however, there is a role for imaging in assisting with staging as this is often a difficult assessment. Treatment should be individualized and depends on stage as well as histologic subtype. It is prudent to refer cases to centers of excellence with experience in dealing with this rare gynecological cancer."

Causes and Risk Factors for Cancer of the Vagina

Scientists have found that certain risk factors make a woman more likely to develop vaginal cancer. But many women with vaginal cancer do not have any apparent risk factors. And even if a woman

with vaginal cancer has one or more risk factors, it is impossible to know for sure how much that risk factor contributed to causing the cancer.

Age - Squamous cell cancer of the vagina occurs mainly in older women. Only 15% of cases are found in women younger than 40. Almost half of cases occur in women who are 70 years old or older.

Diethylstilbestrol (DES) - DES is a hormonal drug that was given to some women to prevent miscarriage between 1940 and 1971. Women whose mothers took DES (when pregnant with them) develop clear-cell adenocarcinoma of the vagina or cervix more often than would normally be expected.

Vaginal adenosis - Normally, the vagina is lined by flat cells called squamous cells. In about 40% of women who have already started having periods, the vagina may have one or more areas where it is lined instead by glandular cells. These areas of gland cells are called *adenosis*. It occurs in nearly all women who were exposed to DES during their mothers' pregnancy. Having adenosis increases the risk of developing clear cell carcinoma, but this cancer is still very rare.

Human Papilloma Virus - Human papilloma virus (HPV) is a group of more than 100 related viruses. They are called papilloma viruses because some of them cause a type of growth called a *papilloma*. Papillomas - more commonly known as warts - are not cancers.

Smoking - Smoking tobacco more than doubles a woman's risk of getting vaginal cancer.

Alcohol - Drinking alcohol might affect the risk of vaginal cancer.

Human immunodeficiency virus - Infection with HIV (human immunodeficiency virus), the virus that causes AIDS, also increases the risk of vaginal cancer.

Vaginal irritation - In some women, stretching of the pelvic ligaments may cause the uterus to sag into the vagina or even extend outside the vagina. This condition is called *uterine prolapse* and can be treated by surgery or by wearing a pessary, a device to keep the uterus in place. Some studies suggest that long-term (chronic) irritation of the vagina in women using a pessary may slightly increase the risk of squamous cell vaginal cancer. But this association is extremely rare, and no studies have conclusively proven that pessaries actually cause vaginal cancer.

Auto immune condition – a condition called systemic lupus erythematosus increases the risk for vaginal cancer.

Women who have had radiotherapy to the pelvic area - may also have a very slightly increased risk.

Other factors - Other factor that may increase the risk of vaginal cancer include:

- Organ transplants.
- Having a history of abnormal cells in the uterus or cancer of the uterus.
- Having had a hysterectomy for health problems that affect the uterus.

Signs and Symptoms of Cancer of the Vagina
Possible signs of vaginal cancer include pain or abnormal vaginal bleeding.

Vaginal cancer often does not cause early symptoms and may be found during a routine pelvic examination and Pap test. When symptoms occur, they may be caused by vaginal cancer or by other conditions. Women are advised to check with a health professional if they have any of the following problems:

- bleeding or discharge not related to menstrual periods
- pain during sexual intercourse
- pain in the pelvic area
- a lump in the vagina
- pain when urinating
- constipation

Diagnosis of Cancer of the Vagina
Screening healthy women for vaginal cancer - Vaginal cancer is sometimes found during a routine pelvic examination before signs and symptoms become evident.

The doctor may also do a Pap test. Pap tests are usually used to screen for cervical cancer, but sometimes vaginal cancer cells can be detected on a Pap test.

Staples, J.N. & Duska, L.R. 2019.
"The Pap smear is the only proven screening intervention in the field of gynecologic oncology. Women should receive treatment for precancerous conditions of the cervix, vulva, vagina, and endometrial lining. Women with inherited conditions should consider having a risk-reducing surgery once they have finished childbearing. The human papilloma virus vaccination should be offered to all girls and boys aged 11 to 12 years, and can also be given as early as age 9 and through 26 years of age."

Other examinations may include:

- Colposcopy is an examination of the vagina with a special lighted magnifying instrument called a colposcope. Colposcopy allows the doctor to magnify the surface of the vagina to see any areas of abnormal cells.
- Biopsy - removing a sample of vaginal tissue for testing. Biopsy is a procedure to remove a sample of suspicious tissue to test for cancer cells. The doctor may take a biopsy of tissue during a colposcopy exam. The doctor sends the tissue sample to a laboratory for testing.

Patient may also have one or more of the following additional tests:

- Chest x-ray and blood tests
- CT (computerised tomography) scan
- MRI (magnetic resonance imaging) scan
- PET scan (positron emission tomography scan)

- Cystoscopy: A procedure to look inside the bladder and urethra to check for abnormal areas.
- Ureteroscopy : A procedure to look inside the ureters to check for abnormal areas.
- Ureteroscopy. A ureteroscope (a thin, tube-like instrument with a light and a lens for viewing) is inserted through the urethra into the ureter. The doctor looks at an image of the inside of the ureter on a computer monitor.
- Proctoscopy: A procedure to look inside the rectum to check for abnormal areas.

Treatment of Cancer of the Vagina
Treatment options for vaginal cancer depend on several factors, including the type of vaginal cancer and its stage. Treatment for vaginal cancer typically may include:

Surgery
Types of surgery that may be used in women with vaginal cancer include:

- Removal of small tumours or lesions.
- Removal of the majority of the pelvic organs (pelvic exenteration).

Radiation therapy
Radiation therapy uses high-powered energy beams, such as X-rays, to kill cancer cells. Radiation can be delivered two ways:

- External radiation. External beam radiation is directed at the entire abdomen or just the pelvis, depending on the extent of your cancer.
- Internal radiation. During internal radiation (brachytherapy), radioactive devices — seeds, wires, cylinders or other materials — are placed in your vagina or the surrounding tissue.

Westerveld, H., Nesvacil, N., Fokdal, L., Chargari, C., Schmid, M.P., Milosevic, M., Mahantshetty, U.M. & Nout, R.A. 2020.
"Primary vaginal cancer is a rare cancer and clinical evidence to support recommendations on its optimal management is insufficient. Because primary vaginal cancer resembles cervical cancer in many aspects, treatment strategies are mainly adopted from evidence in locally advanced cervical cancer. To date, the organ-sparing treatment of choice is definitive radiotherapy, consisting of external beam radiotherapy and brachytherapy, combined with concurrent chemotherapy. Brachytherapy is an important component of the treatment and its steep dose gradient enables the delivery of high doses of radiation to the primary tumour, while simultaneously sparing the surrounding organs at risk. The introduction of volumetric CT or MRI image-guided adaptive brachytherapy in cervical cancer has led to better pelvic control and survival, with decreased morbidity, than brachytherapy based on x-ray radiographs. MRI-based image-guided adaptive brachytherapy with superior soft-tissue contrast has also been adopted sporadically for primary vaginal cancer. This therapy has had promising results and is considered to be the state-of-the-art treatment for primary vaginal cancer in standard practice."

Schmid, M.P., Fokdal, L., Westerveld, H., Chargari, C., Rohl, L., Morice, P., Nesvacil, N., Mazeron, R., Haie-Meder, C., Pötter, R., Nout, R.A. & GEC-ESTRO GYN Working Group. 2020.
Background and aim: External beam radiotherapy (EBRT) combined with brachytherapy has an essential role in the curative treatment of primary vaginal cancer. EBRT is associated with significant tumour shrinkage, making primary vaginal cancer suitable for image guided adaptive brachytherapy

(IGABT). The aim of these recommendations is to introduce an adaptive target volume concept for IGABT of primary vaginal cancer.
Methods: In December 2013, a task group was initiated within GYN GEC-ESTRO with the purpose to introduce an IGABT target concept for primary vaginal cancer. All participants have broad experience in IGABT and vaginal cancer brachytherapy. The target concept was elaborated as consensus agreement based on an iterative process including target delineation and dose planning comparison, retrospective analysis of clinical data and expert opinions.
Results: Gynaecological examination and MR imaging are the modalities of choice for local tumour assessment. A specific template for standardised documentation with clinical drawings for vaginal cancer was developed. The adaptive target volume concept comprises different response-related target volumes. For EBRT these are related to the primary tumour and the lymph nodes, while for IGABT these are related to the primary tumour and are consisting of the residual gross tumour volume (GTV-T_{res}) and the high-, and intermediate risk clinical target volumes (CTV-T_{HR}, CTV-T_{IR}).
Conclusion: This target concept for IGABT of primary vaginal cancer defines adaptive target volumes for volumetric dose prescription and should improve comparability of different radiotherapy schedules of this rare disease. A prospective evaluation of the target volume concept within a multicentre study is planned.

Yang, J., Delara, R., Magrina, J., Magtibay, P., Langstraat, C., Dinh, T., Karlin, N., Vora, S.A. & Butler, K. 2020.
Objective: To analyze clinical characteristics and survival of patients with primary vaginal cancer.
Methods: Retrospective analysis of patients with primary squamous, adenocarcinoma and adenosquamous cell carcinoma of the vagina identified from the Mayo Clinic Cancer Registry between 1998 and 2018.
Results: A total of 124 patients were identified: stage I, 39 patients; stage II, 44, stage III, 20 and stage IV, 21. Patients with stage III and IV were older as compared to stage I and II. (mean ages 61 vs 67) ($p = 0.024$). Squamous cell carcinoma made up 71% of tumors. History of other malignancy was present in 24% patients. Median follow-up time was 60 months (range 1-240). Five-year PFS in stage I, II, III and IV was 58.7%, 59.4%, 67.3% and 31.8%, respectively ($p = 0.039$). Five-year DSS was 84.3%, 73.7%, 78.7% and 26.5% respectively ($p < 0.001$). Advanced stage, tumor size >4 cm, entire vaginal involvement, and lymph node (LN) metastasis were poor prognosticators in univariate analysis. Primary surgery in stage I/II patients had similar survival outcomes as compared to primary radiation, but post-operative RT rate was 55%. Brachytherapy alone was associated with a high local recurrence (80%) in stage I/II patients. The addition of brachytherapy had improved 5-year PFS and DSS than EBRT alone in patients with stage III/IVA. ($p < 0.001$).
Conclusion: Surgery or radiation is effective treatment for vaginal cancer stage I and II. The addition of brachytherapy to external pelvic radiation increases survival in stages III-IV.

<u>Other Options</u>
If surgery and radiation cannot control the cancer, the patient may be offered other treatments, including:

- Chemotherapy. Chemotherapy uses chemicals to kill cancer cells
- Clinical trials

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/ heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Resources and References Consulted or Utilised

Adams, T.S. & Cuello, M.A. 2018. Cancer of the vagina. Int J Gynaecol Obstet. 2018 Oct;143 Suppl 2:14-21. doi: 10.1002/ijgo.12610.

American Cancer Society
http://www.cancer.org/cancer/vaginalcancer/detailedguide/vaginal-cancer-what-is-vaginal-cancer
http://www.cancer.org/cancer/vaginalcancer/detailedguide/vaginal-cancer-risk-factors
http://www.cancer.org/cancer/vaginalcancer/detailedguide/vaginal-cancer-treating-by-stage

Bruni, L., Albero, G., Serrano, B., Mena, M., Gómez, D., Muñoz, J., Bosch, F.X.& de Sanjosé, S. 2019. ICO/IARC Information Centre on HPV and Cancer (*HPV Information Centre*). Human Papillomavirus and Related Diseases in South Africa. Summary Report 17 June 2019. [Date Accessed]

Cancer.Net
http://www.cancer.net/cancer-types/vaginal-cancer/staging

Cancer Research UK
http://www.cancerresearchuk.org/cancer-help/type/vaginal-cancer/about/risks-and-causes-of-vaginal-cancer

eMedTV
http://hpv.emedtv.com/hpv/types-of-hpv.html

Female Reproductive System
http://www.webmd.com/women/vagina

Gómez-Raposo, C., Merino Salvador, M., Aguayo Zamora, C. & Casado Saenz, E. 2020 Adjuvant chemotherapy in endometrial cancer. Cancer Chemother Pharmacol. *Cancer Chemother Pharmacol*. 2020 Jan 16. doi: 10.1007/s00280-019-04027-6. [Epub ahead of print] Review.

Kaltenecker, B. & AlEssa, A.M. 2020. Vaginal Cancer. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Jul 1.

Kombathula, S.H., Rapole, P.S., Prem, S.S. & Badhe, B. 2019. Primary small cell carcinoma of the vagina: a rare instance of prolonged survival. BMJ Case Rep. 2019 Mar 9;12(3). pii: e227100. doi: 10.1136/bcr-2018-227100.

MacMillan Cancer Support
http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Vagina/Vaginalcancer.aspx

Mayo Clinic
http://www.mayoclinic.com/health/vaginal-cancer/DS00812/DSECTION=tests-and-diagnosis
http://www.mayoclinic.com/health/vaginal-cancer/DS00812/DSECTION=treatments-and-drugs

National Cancer Institute
http://www.cancer.gov/cancertopics/pdq/treatment/vaginal/Patient/page1
http://www.cancer.gov/cancertopics/pdq/treatment/vaginal/Patient/page2
http://www.cancer.gov/clinicaltrials/learningabout/what-are-clinical-trials

ObGyn Knowledge Bank
http://www.nuthalapaty.net/kb/creog_display.asp?y=all&q=6-3-D-2

Saeaib, N., Peeyananjarassri, K., Liabsuetrakul, T., Buhachat, R. & Myriokefalitaki, E. 2020 Hormone replacement therapy after surgery for epithelial ovarian cancer. *Cochrane Database Syst Rev*. 2020 Jan 28;1:CD012559. doi: 10.1002/14651858.CD012559.pub2.

Schmid, M.P., Fokdal, L., Westerveld, H., Chargari, C., Rohl, L., Morice, P., Nesvacil, N., Mazeron, R., Haie-Meder, C., Pötter, R., Nout, R.A. & GEC-ESTRO GYN Working Group. 2020. Recommendations from gynaecological (GYN) GEC-ESTRO working group - ACROP: Target concept for image guided adaptive brachytherapy in primary vaginal cancer. *Radiother Oncol*. 2020 Apr;145:36-44.

Senkomago, V., Henley, S.J., Thomas, C.C., Mix, J.M., Markowitz, L.E. & Saraiya, M. 2019. Human papillomavirus-attributable cances – United States, 2012-2016. MMWR Morb Mortal Wkly Rep. 2019 Aug 23;68(33):724-728. doi: 10.15585/mmwr.mm6833a3.

Staples, J.N. & Duska, L.R. 2019. Cancer screening and prevention highlights in gynecologic cancer. *Obstet Gynecaol Clin North Am*. 2019 Mar;46(1):19-36. doi: 10.1016/j.ogc.2018.09.002.

Tumour Grade and Tumour Stage
https://www.medicinenet.com/cancer_101_pictures_slideshow/article.htm

Westerveld, H., Nesvacil, N., Fokdal, L., Chargari, C., Schmid, M.P., Milosevic, M., Mahantshetty, U.M. & Nout, R.A. 2020. Definitive radiotherapy with image-guided adaptive brachytherapy for primary vaginal cancer. *Lancet Oncol*. 2020 Mar;21(3):e157-e167.

Wikipedia
https://en.wikipedia.org/wiki/Vagina

Yang, J., Delara, R., Magrina, J., Magtibay, P., Langstraat, C., Dinh, T., Karlin, N., Vora, S.A. & Butler, K. 2020. Management and outcomes of primary vaginal cancer. *Gynecol Oncol*. 2020 Nov;159(2):456-463.