ORIGINAL ARTICLE

PRIMARY VAGINAL CANCER. RETROSPECTIVE STUDY PERFORMED ON A GROUP OF 23 PATIENTS

Olga Scaleţchi[1], M. Dumitraşcu[1,2]

[1]Obstetrics and Gynecology Department, Bucharest Emergency University Hospital, Romania
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author: Olga Scaleţchi
Phone no.: 0040786415997
E-mail: olgascaletchi@yahoo.com

Abstract

Vaginal cancer is caused by the uncontrolled development of malignant cells in the vagina. Vaginal tumors constitute 1-3% of all primary tumors of the female genital area, predominantly affects postmenopausal women. Symptomatology is nonspecific and occurs most of the time when the tumor has an advanced invasion degree. The most common location of vaginal cancers is in the upper third of the vagina and the most commonly encountered histopathological type is squamous cell carcinoma. It is assumed that the etiology of vaginal cancer is similar to the cervical cancer etiology, the most important factors being HPV (Human Papilloma Virus), DES consumption (diethylstilbestrol), early onset of sexual life and cervical cancer.

Keywords*: vaginal cancer, risk factors*

Introduction

According to the FIGO (International Federation of Gynecology and Obstetricians) definition, primary vaginal cancer is the vaginal injury not involving the external cervical or vulvar opening. There are extremely rare neoplasms with increasing incidence, probably due to the more frequent detection of HPV virus infection in the population. It is crucial to distinguish between primary vaginal cancers and cancers that cause metastasis at the vaginal level (cervical cancer, endometrial cancer, rectal cancer or bladder cancer) because approximately 80% of vaginal tumors are of metastatic origin. There are 4 histological types of vaginal cancer. The most common histological type is squamous cell carcinoma (80%). It develops from flat epithelial cells in the upper third of the vagina with multifocal aspect [1]. Adenocarcinoma is much rarer, it occurs in approximately 14% of cases, develops from vaginal glandular cells.

Four types of vaginal adenocarcinomas are described: Clear cell adenocarcinoma occurs in young women aged 15-30 years with a history of in utero exposure to diethylstilbestrol. Mucinous adenocarcinoma is characterized by the presence of mucus around neoplastic cells. Papillary adenocarcinoma develops from perivaginal connective tissue. Adenoscuamos carcinoma combines squamous and glandular cells it is extremely aggressive, only 8 cases have been described in the literature [2]. Primary vaginal sarcoma accounts for 4-5% of vaginal cancers. It is characterized by a rapid growth with the origin from the vaginal muscle tissue. Leiomyosarcoma, rhabdomyosarcoma, mullerian mixed sarcoma, embryonic rhabdomyosarcoma and botryosarcoma are histopathological forms of vaginal sarcoma. Vaginal melanomas are rare

tumors, approximately 9% of vaginal tumors. They appear predominantly in patients over 60 years of age. Often diagnosed late, leading to a 5-year survival of approximately 10-20%, can easily be called the cancer with the worst prognosis of all vaginal cancers. Melanomas tend to locate in the lower part of the vagina. From a histopathological point of view, vaginal melanomas are identical to melanomas with other localizations.

Risk factors involved in the development of vaginal cancer are advanced age [3,4]. Early beginning of sexual life, multiple sexual partners are circumstances that correlate with HPV infection. HPV infection in some patients leads to precancerous lesions that in time can produce vaginal cancer [5]. Cervical cancer increases the risk of vaginal cancer by 3 times, irradiated patients having a higher risk of developing neoplasia compared to unirradiated patients. A history of hysterectomy has been associated with increased risk of vaginal cancer [6].

It is clinically manifested by postmenopausal bleeding or bleeding after sexual intercourse. Patients may experience pain during intercourse or may have non-specific leukorea, initially being whitish than may become pinkish or bad smelling [7]. If the tumor has invaded the bladder clinically appears dysuria, increase of urinary frequency, hematuria or urinary retention. Large tumors that develop on the posterior wall of the vagina can cause rectal tenesmus, constipation, appearance of blood in feces.

Clinical examination, Babeş-Papanicolau exam, colposcopy, vaginoscopy brings important clinical elements that can determine the clinician to suspect a pathology in the vagina. The diagnosis of certainty is based on the histopathological examination. Vaginal cancers are staged according to FIGO criteria and TNM staging system of American Joint Committee on Cancer (AJCC) [8].

Materials and methods

This writing is a retrospective statistical study in the period of 2005 - 2015. In order to achieve this, we used information from observation charts. The study was conducted on 23 women with vaginal cancer patients of the University Emergency Hospital Bucharest, the gynecology department.

The inclusion criteria were:

- The presence of abnormal cellularity in the vagina that does not involve the external cervical or vulvar opening,
- Vaginal cancer that occurred 5 years after successful cervical cancer treatment.

The exclusion criteria were:

- Cancers occurring at the vaginal level following an extension from the adjacent genital areas
- Extragenital tumors metastasized to the vagina
- Tumors that have spread from the vaginal fornix to the cervical opening,
- Tumors including the cervix or vulva.

For the study we used data obtained from:

- Complete clinical examination
- Gynecological examination
- Babeş-Papanicolau cytology
- Imaging investigations
- Histopathological examination of the lesion.

Results

The study dealt with the research group of patients who had vaginal cancer aged between 23 and 81 years. Distribution of cases by age group showed that the patients in the age groups 41-60 and 61-80 had the highest incidence of vaginal cancer (Figure 1).

No patient with vaginal cancer was nulipara, most of them had two or more children (Figure 2).

In the studied group, the presentation to the physician was due to metrorrhagia occurring between periods of menstrual cycle or metrorrhagia after menopause. Most of the patients had metrorrhagia as a single sign. Others simptoms associated with metrorrhagia were pelvic pain, abundant leucorrhea, dyspareunia associated with dysuria and constipation (Figure 3).

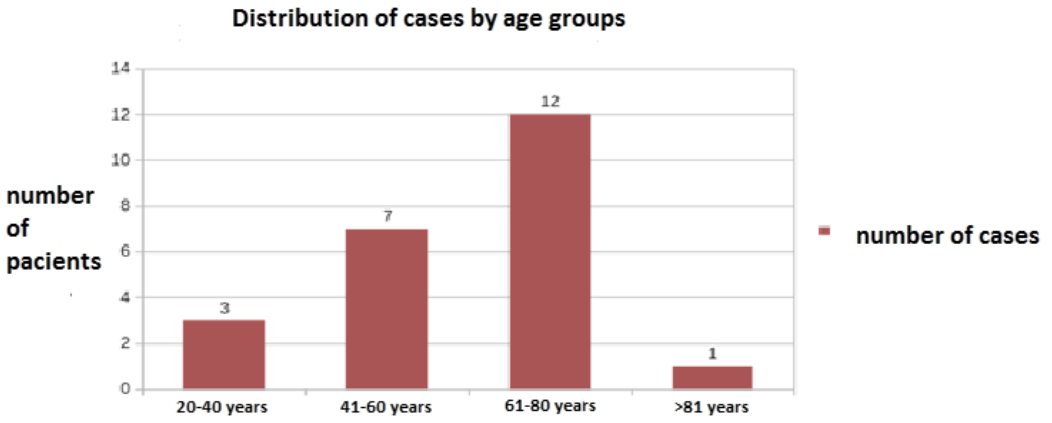

Figure 1 - Batch distribution by age groups

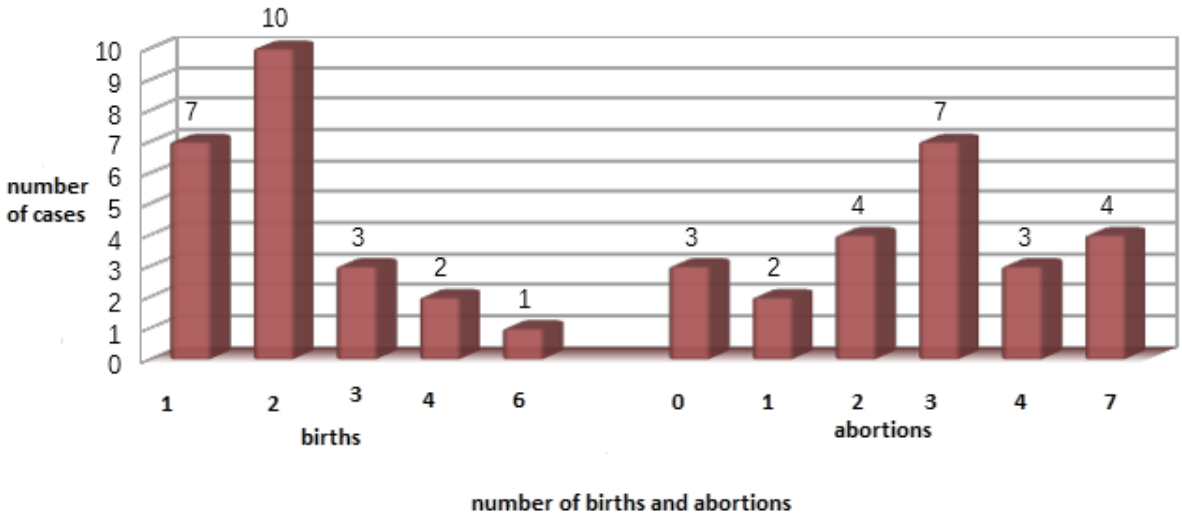

Figure 2 - Number of births and abortions

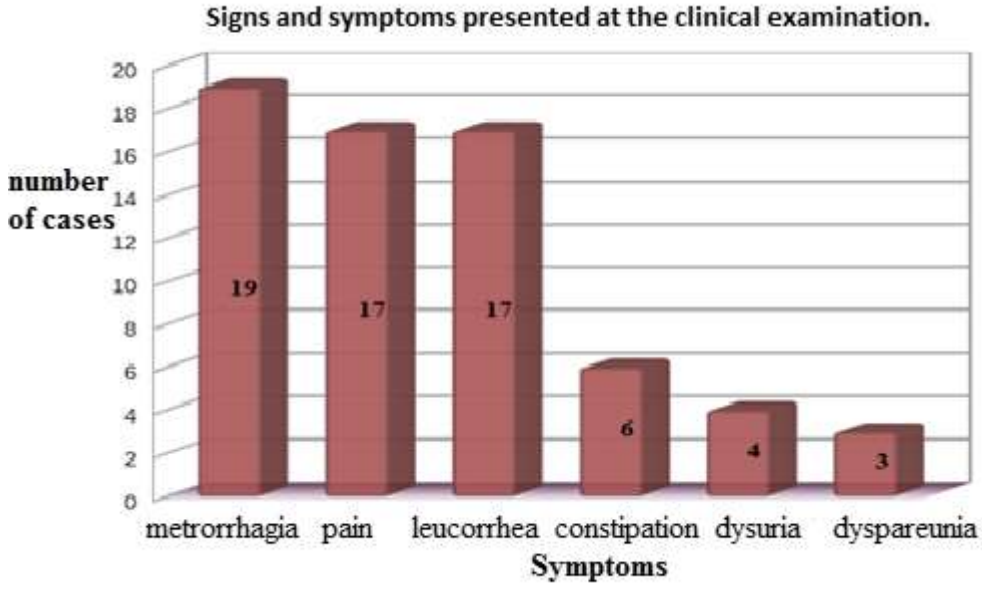

Figure 3 - Signs and symptoms presented at the clinical examination

Following the examination with valves and vaginal ink, various lesions on the vaginal surface were identified.17 cases with upper third vaginal lesions were found, 4 cases with injuries in the middle of the vagina and 2 with injuries in the lower part of the vagina (Figure 4). We can see that the upper third of the vagina is the most affected area. The macroscopic appearance of lesions in vaginal cancer can be ulcerated or exophytic, the mucous membrane may have a stiff, thickened, rigid or edematous appearance.

In the study, 8 of the patients had lesions with ulcerated appearance, 6 had necrosis areas on the lesion's surface, in four cases the suspect area had an inflamed and infiltrated appearance, and in the other 5 cases the macroscopic aspect of the lesions was unknown.

The lesions identified at the clinical examination were biopsied and sent to the physician of pathological anatomy for diagnosis. Following the histopathological examination, the cellular nature of the tumors was identified. In 18 cases the diagnosis of squamous cell carcinoma was diagnosed, in 4 cases the diagnosis of adenocarcinoma and in a case of clear cell adenocarcinoma (Figure 5).

Following the anamnesis and the clinical examination, we tried to identify the risk factors that could lead to the appearance of vaginal cancer (Figure 7). Within the studied group the following etiological factors were highlighted:

•Old age • Early sexual life • Multiple sexual partners •Smoking • Alcohol consumption

• HPV infection • Cervical cancer in the past • History of Radiotherapy • Chronic infections of the vagina.

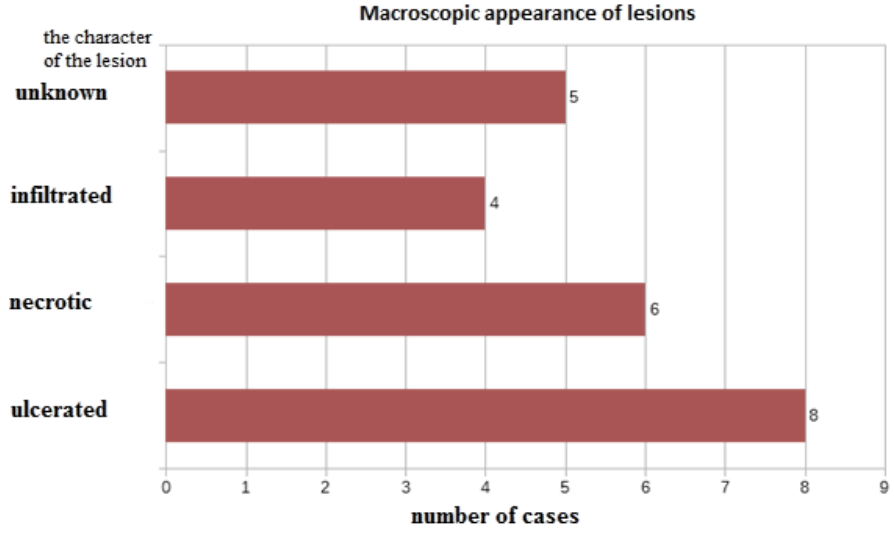

Figure 4 - Macroscopic appearance of lesion

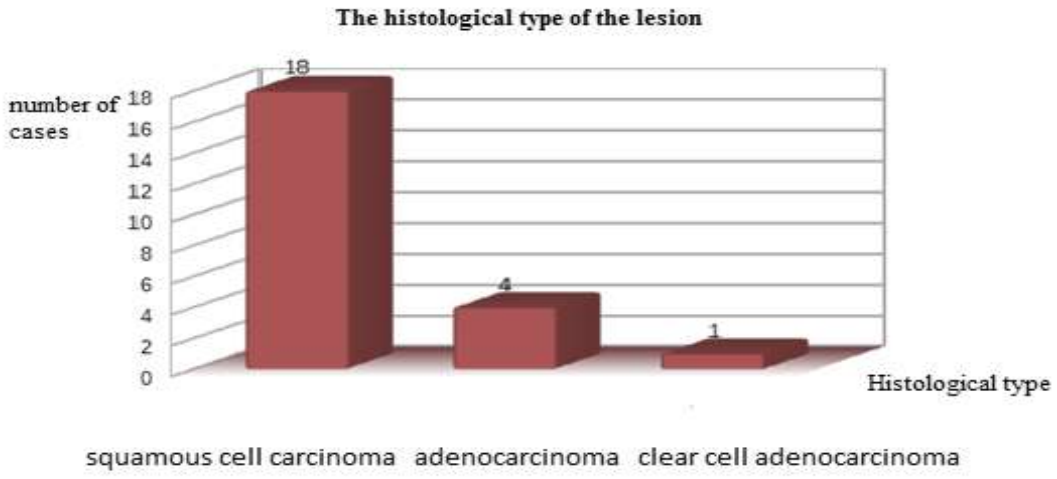

Figure 5 - Histopathologic type of lesion

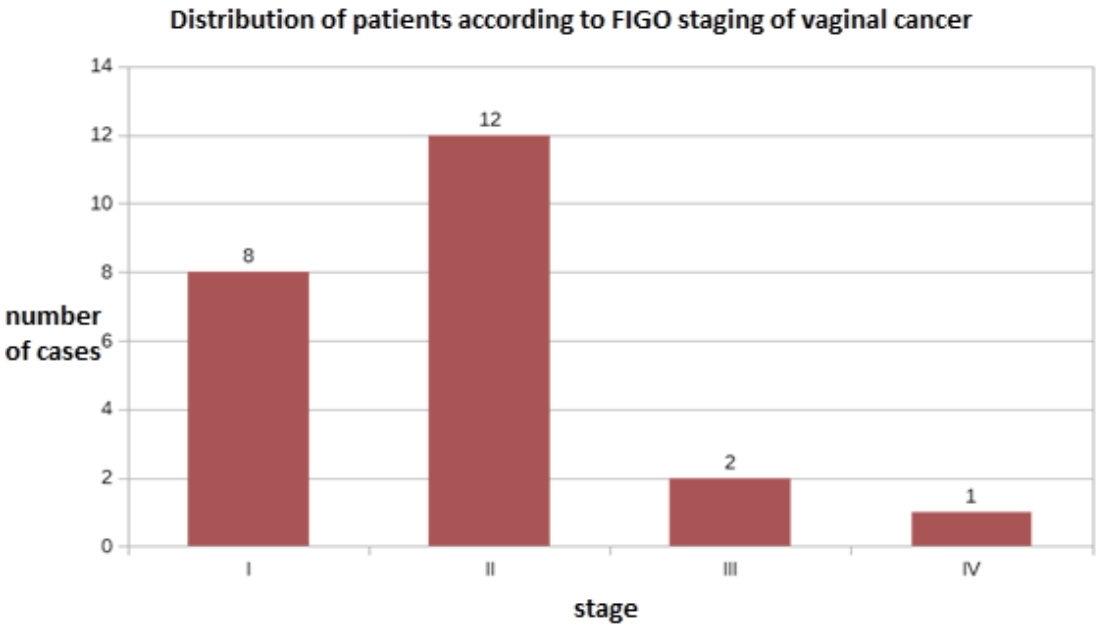

Figure 6 - Distribution of patients according to FIGO staging of vaginal cancer

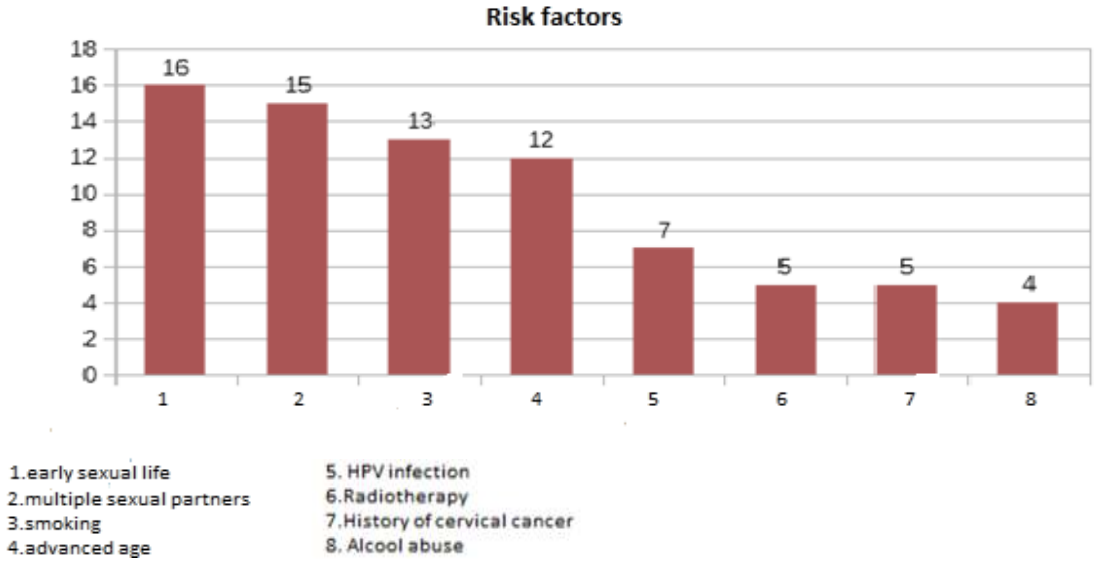

Figure 7 - Risk factors identified in the studied lot

Discussions

Primary vaginal cancer is a rare disease, representing about 1-3% of all malignant pathologies of female genitalia [9] . It was first described as a single entity by Graham and Meigs in 1952. Due to the reduced frequency of the condition, there is very little information about the natural history of the disease, the prognosis and the treatment. It usually affects women over 60 and is frequently located in the upper third of the vagina [10]. The Survival Rate of patients with vaginal cancer is generally low, this correlates with the staging of the disease and according to some authors with the size of the lesion. Survival is reduced in patients older than 60 years, symptomatic at the time of diagnosis, having injuries in the middle or lower third of the vagina or developing poorly differentiated tumors. It is considered that the site of the lesion does not affect the prognosis, however the damage to the whole vaginal surface assumes a poor prognosis.

Currently, we know the following risk factors that contribute to the appearance of vaginal cancer: **Age** Squamous cell cancer predominantly occurs to older women. Only in 15% of cases is found in women younger than 40 years. Approximately half of vaginal cancers occur in women over 70 years of age. **Diethylstilbestrol (DES).** DES is a hormonal

drug that was administered between 1940 and 1971 to prevent spontaneous abortions. Women whose mothers took DES while they were pregnant have an increased risk of developing clear cell adenocarcinoma of the vagina and cervix [11]. Approximately one in 1,000 daughters of mothers taking DES develops clear cell adenocarcinoma. The risk appears to be increased if pregnant women used the medicine during the first 16 weeks of pregnancy [12]. **Human papilloma virus (HPV)** is a group of about 200 viruses. There are strains with high oncogenicity and low oncogenic strains. The high oncogenic strains are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68, 82, 26, 53, 66. Lowered oncogenic strains are: 6, 11, 40, 42, 43, 44, 54, 61, 72, 81. Of all these types listed above, the most responsible strains for cancer are 16 and 18. The transmission pathway of the virus is the sexual one, the CDC believes that about 80-90% of sexually active women and males will become infected with Human Papilloma Virus at a time of life. HPV virus infects epithelial cells and begins to secrete proteins that cells integrate into their structure. Two of the proteins secreted by the virus (E6 and E7) interfere with cell function that normally prevents excessive growth, so infected cells are determined to grow aberrantly and stop apoptosis. Frequently, immune cells find infected structures and eliminate them, transient disease, but there are situations when the immune system cannot cope with the infection, so it gets persistent. Persistent infections are responsible for the appearance of paraneoplastic and neoplastic lesions.

Cervical cancer and cervical dysplasia increase the risk of developing vaginal cancer with squamous cells probably because of common risk factors such as HPV infection or smoking. Some studies have suggested the possibility of vaginal cancer arising from radioactive treatment for cervical cancer [13]. **Smoking** Smokers have twice the risk of vaginal cancer than non-smokers.

Alcohol consumption can cause vaginal cancer. A study on a group of alcoholic women identified more cases of vaginal cancer than expectations. Unfortunately, no risk factors such as HPV infection or smoking have been considered in this study. A more recent study that took into account associated risk factors has concluded that women who have never consumed alcohol have the risk of developing vaginal cancer lower than other women. **HIV** infection Human immunodeficiency virus infection is thought to increase the risk of vaginal cancer. **Vaginal irritation** Long-term vaginal irritation can cause cancer. This situation can be experienced in women with uterine prolapsed with special devices supporting the uterus. Some studies claim that long-term use of pessaries causes chronic inflammation at the vaginal level and may lead to neoplastic lesions over time.

Diagnosis of vaginal cancer can be done by clinical and paraclinical methods. The clinical examination consists of a thorough examination of the gynecological and obstetric anamnesis followed by examination of the vagina with a speculum and the execution of the vaginal and rectal touch. Paraclinic examinations helps the clinician. An abnormal Pap smear may suggest the presence of squamous cell lesions. In the case of clear cell adenocarcinomas, cytological diagnosis can only account for 33% of cases, due to growth pattern, namely submucosal invasion. When a pathological smear is detected, the physician should first exclude the presence of cervical cancer, given its increased incidence. If the patients had a hysterectomy in the past, then vaginal colposcopy is indicated. If no lesion is identified then the entire vaginal blunt must be excised because the lesion can be hidden on the vaginal suture [13]. Vaginal colposcopy-Lugol solution can help detect areas requiring biopsy because, after applying the solution to normal vaginal tissue it becomes dark brown, but the malignant tissue does not stain. For the reaction to occur, healthy vaginal tissue should be estrogenized and with sufficient glycogen content.

Biopsy is indicated that all suspicious vaginal lesions. It should be performed with instruments similar to those used for cervical biopsy. The Tischler forceps biopsy is the diagnosis of certainty, based on which the tumor can be framed in a histological type. For advanced tumors, cystoscopy and colonoscopy can be used to assess the lesion invasion limits. The imaging methods available to the clinician are varied but unspecific.

Radiological examination can be useful for remote metastasis diagnosis. Computer tomography can provide information on the location, size and shape of the tumor, is useful in identifying large lymph nodes that can be invaded by tumor cells or remote metastases. When computerized tomography does not provide sufficient data, nuclear magnetic resonance is the most useful instrument for vaginal analysis, it has the ability to differentiate the tumor of vaginal fibrosis [14]. Positron emission tomography is useful in identifying metastasis in the lymph nodes or remote metastases. Screening for early diagnosis of vaginal cancer has not yet been elaborated. It is considered that the clinical examination and the Pap smear test is sufficient to suspect a lesion with a high risk of malignancy. Prudent screening of patients who have a history of vulvar or cervical cancer is recommended because the risk of developing vaginal cancer is very high. Patients who have undergone a hysterectomy for a cervical pathology have the recommendation to perform regular gynecological control [15].

Treatment of vaginal cancer differs according to staging.

Stage I

Radiotherapy is often said to be the treatment of choice in stage I tumors because surgery requires satisfactory safety margins that can be achieved by total vaginectomy or pelvic exenterance. Early-stage tumors involving the posterior wall of the vagina in the upper third can be removed by radical hysterectomy and partial vaginectomy if the uterus is intact or by superior radical vaginiectomy if the patient was previously subjected to a hysterectomy. In both cases, bilateral lymph node ellipse [16] is performed.

Stage II

The most used method of treatment is radiotherapy. It has been found that radical surgery does not give better results than when patients are only treated with radiotherapy. Radical vaginectomy is indicated in most cases in patients who have been exposed to pelvic radiotherapy [17,18].

Stage III and Stage IVA

The 5-year survival rate of patients with stage 3 tumors is 30-60% and those with stage IVA of 15-40%. Tumors of Stage III and IVA are massive, infiltrative, involve the entire vaginal wall, pelvic wall, bladder and rectum. The extension pattern of these tumors and the close relationships with healthy tissue make surgery difficult and require advanced surgical capabilities. Pelvic recurrences are common and the risk of remote metastasis has an increased rate [19].

Patient survival rate is generally low, correlates with disease staging and lesion size. It is considered that the survival of patients older than 60, symptomatic at the time of diagnosis, with lesions in the middle or lower third of the vagina is low. The survival rate at 5 years is considered to be 84% for stage I, 74% for stage II and 57% for stage III and IV [20].

Conclusions

The present study aims to identify the risk factors and treatment methods that can be addressed in vaginal cancer. The group consists of 23 patients aged between 26 and 81 years who come from the University of Emergency Hospital of Bucharest. The study was a retrospective based on observation sheets from 2005-2015.

Vaginal cancer is among the rarest oncological pathologies. This can be supported by the number of cases encountered in the last 15 years in the clinic. • The average age of the diagnosis was 58.65 years. Most patients from urban areas. Recently, malignant vaginal tumor has been observed in younger patients due to HPV infection.

Symptomatology present at admission was unspecific, neglected by patients for a long time. The predominantly identified histopathological type was squamous cell carcinoma. Clinical and paraclinical examinations are crucial to identify the pathology and its proper staging. • We cannot say for sure what the etiology of vaginal cancer is, but we can assume that certain risk factors can cause this pathology.

Among the risk factors identified in the study group we can list: advanced age, early onset of sexual life, multiple sexual partners, smoking, alcohol consumption, HPV infection, past cervical cancer.

A specific approach is needed that corresponds to the staging of the disease. The currently available treatment for vaginal cancer is radiotherapy, radiation therapy associated with chemotherapy and surgery.

In all cases, the multidisciplinary approach is essential, consisting of a gynecologist, an oncologist and a radiologist.

Surgery for the pathology of the vaginal sphere is extremely mutilating, therefore it is recommended when it is possible to reconstruct the vagina and to offer psychiatric support for patients.

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