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REVIEW ARTICLE

Primary carcinoma of the vagina

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Summary

In this paper we reviewed the risk factors for primary carcinoma of the vagina (PCV), diagnostic and therapeutic modalities, and principles leading to rational decision-making in the individualized management of vaginal carcinoma patients.

The review was based on the recent literature and our own years- long experience with the disease. PCV is a rare gynecologic malignancy accounting for about 2% of all neoplasms of the female genitals. Most of the affected women are over 60 years of age, peaking between 70 and 80 years. Only 10-15% of patients are below 50 years. Histopathologically, most common are squamous cell carcinoma (80-90%) and adenocarcinoma (4-10%).

The leading risk factor for vaginal intraepithelial neoplasia (VAIN) and subsequent squamous cell vaginal carcinoma is long-lasting infection with human papillomavirus (HPV) type 16. Prognosis of the disease depends on several factors, the most important of which are age, histologic type, and tumor stage. Survival depends on the disease stage. Five -year survival rates are about 95% for stage 0, 75% for stage I, 60% for stage II, 35% for stage III, 20% for stage IVa, and 0% for IVb stage.

Due to its being a rare entity, there are still controversies as to the most optimal treatment. Individualized treatment approaches have been increasingly used. In most centres, standard treatment for this cancer is radiotherapy. Some reports have shown that surgery might also be an option, while in some centres radiation is supplemented by cisplatin-based chemotherapy. The supposed advantage of radiotherapy is the preservation of the anatomy and function of the vagina. We believe that there are certain psychologic benefits with the preservation of the vagina, regardless of its function. However, preservation of the vaginal function after treatment of invasive vaginal cancer is a rare phenomenon, both in the literature and from our own experience.

Key words: carcinoma, diagnosis, prognosis, therapy, vagina

Introduction

Primary carcinoma of the vagina (PCV) was first described by Cruveilhier in 1826 at the Anatomical Society in Paris. There were only 57 cases described in the literature up to 1890, however without effective treatment. PCV is a rare disease, accounting for 1-2% of all gynecologic malignancies. According to FIGO (International Federation of Gynecology and Obstetrics) criteria, carcinoma of the vagina is defined as a primary disease if it involves only the vagina without invasion of the uterine cervix, vulva or urethra. In cases of concomitant involvement of the uterine cervix and vagina, vulva and vagina, or urethra and vagina, the tumor is classified as primary carcinoma of the uterine cervix, vulva, or urethra [1].

Vagina is more commonly affected by the tumors spreading from adjacent organs. Metastatic carcinoma of the vagina originates from the uterine cervix (32%), endometrium (18%), ovaries (9%), vulva (6%), and urinary tract (4%). Some of them spread directly and some others are distant metastases. Vaginal cancer incidence is 0.7 per 100,000 women. This carcinoma is most common in South America, India, and in African Americans in the U.S.A., and the lowest incidence has been registered in Jewish women. In over 20% of the cases vaginal carcinoma can occur simultaneously with VAIN III. Sarcomas and melanomas of the vagina are extremely rare malignant tumors, while botryoid sarcoma occurs in girls below 5 years of age [2].

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Etiology and risk factors

The etiology of vaginal carcinoma has not yet been fully elucidated, but it is supposed that it is similar to the etiology of cervical cancer [3]. Several case-control studies have been conducted to elucidate the etiology and risk factors for vaginal carcinoma; however, their results have been to an extent contradictory [4-6]. Long-lasting infection with HPV is the leading risk factor for VAIN and subsequent squamous cell carcinoma. Vaginal carcinoma incidence in younger women shows a statistically significant correlation with HPV infection of the genital organs and intraepithelial neoplasms of the uterine cervix [7]. The period of progression of VAIN into invasive carcinoma has not been established. It has been proven that in vaginal cancer patients HPV infection -most commonly with type 16-is present in 21-76% of the cases (53% on average) [8]. In addition to the leading risk factors for vaginal carcinoma, HPV infection, cervical intraepithelial neoplasia (CIN) or VAIN, some other risk factors are also important [9].

In older individuals, vaginal carcinoma correlates with hormonal factors (late menarche) and vaginal traumas [10]. Low socio-economic status (poverty, lack of education) is associated with a higher incidence of vaginal carcinoma. Similarly to cervical cancer, the risk increases with early sexual life, multiple partners, smoking and alcohol. Late menarche (after 14 years of age) and early menopause (before 45) are also of significance. Multiparity can also be a risk factor in the context of the hypothesis that vaginal traumas occur during delivery. On the other hand, nulliparity is also thought of as a risk factor, since it may occur as a consequence of inflammatory diseases in the pelvis caused by sexually transmissible infectious agents, which themselves are risk factors for vaginal cancer [11]. The possible etiological factors are summarized in Table 1.

Immunosuppression is thought to be a possible risk factor, since vaginal carcinomas have been found in women on corticosteroid therapy for longer periods of time [12]. Previous carcinoma of other genital organs increases the risk of vaginal cancer. A number of authors supports the view of multicentric nature of primary gynecologic neoplasms [13]. Little is known about genetic predisposition for vaginal carcinoma, but in 25% of the cases with multiple gynecologic cancers there is a family history of carcinoma [14]. Hysterectomy for dysplasia or neoplasm, especially before the age of 40, is followed by later vaginal carcinoma in 37% of the cases. The etiological background for the onset of vaginal cancer is the same as for those in the cervix or the body of the uterus, and/or the residual cancer in the upper parts of the vagina in cases with positive margins. However, if we consider the multicentric characteristics of the disease, clear margins after surgical resection do not always mean that the tumor is completely excised [15]. In individuals in whom hysterectomy has been carried out for benign lesions the risk of vaginal cancer is not increased [16]. Previous pelvic radiation therapy for uterine cervix carcinoma increases the risk for vaginal carcinoma and sarcoma, especially in women under 40 years. In these cases the latency period ranges from 10 to 40 years [17]. Chronic irritation and vaginal trauma in prolapse, and long-lasting presence of vaginal pessary lead to continual epithelial trauma and subsequent malignant transformation of epithelial cells, producing VAIN and later invasive carcinoma [18].

Modes of spread

Vaginal carcinoma spreads primarily by local invasion. A thin vaginal wall and extensive lymphatic network enable rapid growth and early spread into the adjacent lymph nodes and paravaginal tissues, with rectal, urethral and bladder involvement. In advanced cases fistulas may occur with the adjacent organs. Tumors of the upper vaginal portions spread to pelvic nodes, while tumors of the lower vaginal portion spread to pelvic and inguinal nodes. Blood-borne spread is unusu-

Table 1. Summary of risk factors for primary vaginal carcinoma

Risk factors	*Other risk factors*	*Possible risk factors*
Age [11]	Other gynecological dysplasia and neoplasia [9,13]	Immunosuppression [12]
Previous CIN, VAIN, and/or neoplasia of the cervix [3]	Smoking [11]	Nulliparity [11]
Previous hysterectomy [10]	Low socioeconomic status [11]	Estrogens [12]
HPV (and others STD) [7]	Previous pelvic irradiation [17]	Older age at menarche [11]
	Unstable marital status [11]	Younger age at menopause [11]
	Number of sexual partners [11]	Other malignancies [18]
	Younger age at first intercourse [11]	
	Vaginal trauma from pessaries, prolapse, multigravid and/or hygienic factors [11,18]	

HPV: human papillomavirus, STD: sexually transmitted diseases, CIN: cervical intraepithelial neoplasia, VAIN: vaginal intraepithelial neoplasia

al. Most common distant metastatic sites are the lungs, liver and bones [19].

Symptoms and clinical presentation

The most common symptoms of vaginal carcinoma are increased secretion and bleeding. About 70% of patients have painless bleeding, often occurring after the intercourse or gynecologic examination. However, 10-15% of patients are asymptomatic, mostly those with early vaginal carcinomas diagnosed at routine gynecologic examination or after cytology of the vaginal smear (PAP test) within the frame of screening for cervical carcinoma [20].

Vaginal carcinoma is associated with dyspareunia (painful sexual intercourse), pain in the perineal region and, in advanced disease, pelvic pain too. Since the neck of the bladder is quite close, bladder pain is also a possibility, as well as frequent urination and other urinary tract symptoms, occurring earlier during the course of this disease compared to cervical carcinoma. Urethral involvement with tumor localized in the anterior wall of the distal part of the vagina produces urinary obstruction and extrarenal renal insufficiency. Tumors situated in the posterior wall of the distal part of the vagina produce tenesmus, obstipation, and bloody stools. If extensive involvement of the bladder and/or rectum occurs, vesicovaginal, rectovaginal and vesicorectovaginal fistulae may result [21].

Diagnosis

In all patients treated for CIN or invasive carcinoma of the uterine cervix, there is an increased risk of vaginal carcinoma. Careful vaginal examination and PAP testing are therefore mandatory, especially if there is any suspicion of the disease. Vaginal carcinoma most commonly occurs in the upper third of the vagina, more frequently in the posterior wall, as an exophytic (polypoid, fungiform) growth, or as an endophytic lesion. Later in the disease course larger ulcerations can be observed.

Routine gynecologic examination cannot always detect changes in the vagina, especially if these are small or situated in distal portions, which can be covered by speculum. Some authors think that even up to 20% of these lesions are not identified on routine gynecologic examination [22].

Each suspect location in the vagina should be sampled for cytology and biopsy for histologic confirmation or exclusion of vaginal carcinoma. In older women with vaginal stenosis and, commonly, advanced disease stages, biopsy and clinical staging is recommended to be performed under general anesthesia. For larger tumors in the anterior vaginal wall urethroscopy and cystoscopy are also required; rectoscopy is done for tumors involving the posterior vaginal wall. In certain cases diagnosis is supplemented with computerized tomography (CT) or magnetic resonance imaging (MRI) of the small pelvis. If vaginal lesions are not visible to the naked eye and cytology is abnormal, examination should be supplemented by careful colposcopy and suspect places should be Lugol-stained (atypical epithelium will not be stained). If there are suspect cervical changes or cytology is abnormal, the whole vagina should be checked for possible multifocal lesions. Special attention should be paid to the vaginal suture after hysterectomy. Every clinical and cytologic suspicion should be histopathologically confirmed on bioptic material [23].

New diagnostic imaging techniques

After bioptic confirmation of vaginal carcinoma, the presence of distant and lymphatic metastases should be assessed by way of diagnostic imaging techniques. Lymph node metastases of vaginal carcinoma are similar to those in cervical carcinoma, except in the cases when tumors invade the distal third and spread to the inguinal lymph nodes, similar to vulvar carcinoma.

Positron emission tomography (PET) with glucose analogue (18F)-fluoro-2-deoxy-D-glucose (FDG) is an imaging method based on metabolic rather than on anatomic changes for disease detection. The metabolic characteristic on which oncologic use of FDG-PET is based is the increased presence of glucose in most neoplastic cells. The ability of FDG-PET to detect metastases in normal-sized lymph nodes is much higher compared to conventional imaging (CT, MRI).

FDG-PET is nowadays a standard imaging technique of lymph node staging and detection of metastatic disease in cervical carcinoma. Since cervical and vaginal carcinoma are similar, FDG-PET has become a standard evaluation technique for vaginal carcinoma as well [24].

FIGO staging

Staging of vaginal carcinoma is only clinical, with the exception of stage IV disease. Errors are possible in vaginal carcinoma staging. Carcinoma *in situ* is a stage 0 disease (VAIN 3). Clinical stage I involves tumors confined to the vaginal wall with exophytic growth, sized below 1 cm, while stage II involves tumors with infiltrative growth and invasion of paravaginal tissues.

Some authors have modified the FIGO classification and subdivided stage II in the following manner: A – disease invading only paravaginal tissues; B – parametrial infiltration [25]. Stage III vaginal carcinoma invades the pelvic wall. Stage IV-A disease invades bladder and/or rectum and/or adjacent organs. Stage IV-B disease implies distant metastases. This classification does not differentiate clinical stages based on the involvement of inguinal lymph nodes, despite differences in 5-year survival. However, the TNM classification does take into account the presence of metastases in regional lymph nodes [26].

Prognostic factors

Independent prognostic factors in vaginal carcinoma are disease stage, histologic differentiation, lymph node status, and age at diagnosis. Combination of these factors has a higher predictive value regarding final disease outcome. However, multiple regression analysis has shown that age at presentation and tumor size are the most important prognostic factors; advanced age and larger tumors imply poor prognosis. Tumors below 5 cm in size have the best prognosis. Studies assessing tumor histology, histologic grade and tumor site as prognostic parameters have had contradictory results, demonstrating that vaginal adenocarcinoma has poorer prognosis than squamous cell carcinoma, which has not been confirmed in other studies [14]. As for the histologic degree of tumor differentiation, there is a notion that poorly differentiated tumors have the worst prognosis. Tumors situated in the upper vaginal portions have better prognosis compared to those in the lower portions, but even here there are reports negating the difference (Table 2) [27].

The knowledge acquired so far about etiology, treatment, and prognostic factors of vaginal carcinoma is based on retrospective studies involving limited numbers of cases; in the future, multicentric, prospective studies should assess in more detail various aspects of the disease, including its predictive and prognostic factors (Table 3).

Fundamentals of the treatment of vaginal carcinoma

Since therapeutic management of vaginal carcinoma has not been precisely defined, nor there has been a general consensus in that regard, it is very important for patients to be referred to specialized institutions. The treatment of vaginal carcinoma requires a high degree of individualization, probably the highest of all tumors of the female genitals, since it is a rare entity where the approach is primarily based on disease stage, tumor size, tumor site, and general patient health. In treatment planning, it is important whether the uterus has been removed or not, as well as previous radiotherapy (mostly for cervical carcinoma). Generally, the results of vaginal carcinoma treatment are modest, except for earliest disease stages (Table 4) [28].

Treatment of vaginal intraepithelial neoplasia (VAIN)

For preinvasive lesions of the vagina, treatment is administered in accordance to the degree of VAIN. For VAIN 1, treatment is unnecessary in most cases, since these lesions often heal spontaneously. In VAIN 2, ablative treatment methods are used, most commonly laser therapy. In VAIN 3, laser is utilized, as well as electrocoagulation, but excision is the best approach if the lesion site is appropriate for the intervention. VAIN lesions often situate in the corners of the vaginal suture as a con-

Table 2. Number, stage and age distribution of patients treated for primary carcinoma of the vagina in the period 1999-2008 at the University Clinic of Obstetrics and Gynecology and Clinic of Oncolgy, Nis*

FIGO stage	*Patients n (%)*	*Age distribution (years)*						
		<30	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*>80*
					n (%)			
		1 (2.5)	1 (2.5)	3 (7.5)	7 (17.5)	15 (37.5)	9 (22.5)	4 (10)
Ca *in situ*	2 (5)							
I	8 (20)							
II	10 (25)							
III	18 (45)							
IV	2 (5)							
Total	40 (100)							

*From 1999 to 2008 there were 3.907 gynecological malignancies, but only 40 (1.024%) of them were primary carcinoma of the vagina (12 [30%] younger than 60, 28 [70%] older than 60 years)

Table 3. Histologic type of primary carcinoma of the vagina at the University Clinic of Obstetrics and Gynecology and Clinic of Oncology, Nis

Histologic type	*Patients, n (%)*
Squamous cell carcinoma	32 (80)
Adenocarcinoma	2 (5)
Adenosquamous carcinoma	1 (2.5)
Papillary carcinoma	1 (2.5)
Mucinous carcinoma	1 (2.5)
Angiosarcoma	1 (2.5)
Sarcoma	1 (2.5)
Undifferentiated carcinoma	1 (2.5)
Total	40 (100)

Table 4. Histologic grade of primary carcinoma of the vagina at the University Clinic of Obstetrics and Gynecology and Clinic of Oncology, Nis

Histologic grade	*Patients, n (%)*
I	4 (10)
II	14 (35)
III	4 (10)
IV	18 (45)
Total	40 (100)

Table 5. Treatment modality of primary carcinoma of the vagina at the University Clinic of Obstetrics and Gynecology and Clinic of Oncology, Nis

Treatment modality	*Patients, n (%)*
Radiotherapy only	25 (62.5)
Surgery only	4 (10)
Primary surgery, then radiotherapy	6 (15)
Palliative therapy	5 (12.5)
Total	40 (100)

sequence of hysterectomy. Multifocal vaginal lesions present the most difficult problems for both clinicians and patients with VAIN. Total vaginectomy or radiation therapy are performed in these cases (Table 5) [29].

Surgical treatment

Surgical treatment of vaginal carcinoma was first described in 1890s, and the conclusion of most authors was that surgery is useless in these cases. Back in 1900, the procedure devised by Ernst Wertheim for cervical carcinoma, was introduced for vaginal carcinoma too [30]. For advanced stages, Alexander Brunschwig described in 1948 an exenterative surgical procedure which involved removal of vaginal carcinoma with complete excision of the pelvic visceral organs. However, perioperative morbidity and mortality were very high [31].

Due to the discouraging results of surgery and the proximity of intrapelvic organs to the vagina, radiotherapy has been adopted as principal treatment option. Surgery has had limited use since tumors often cannot be completely removed without complications. The radicality of surgery and radiotherapy is compromised by the anatomical position of the vagina, closeness of urethra, bladder, and rectum. For most of the patients, preserved function of the vagina is a desired treatment outcome, which is an additional treatment planning problem. Surgery for vaginal carcinoma is undertaken in the following cases: clinical stage I; younger women in whom radiation therapy is to be administered; some cases with clinical stage IV disease, especially those with rectovaginal or vesicovaginal fistulas; patients with disease relapse after radiotherapy [32].

In patients with FIGO I disease stage, especially if the tumor is situated in the upper third of the vagina and the uterus is intact, it is necessary to perform radical hysterectomy with bilateral pelvic lymphadenectomy and partial vaginectomy. In cases with previous hysterectomy, partial vaginectomy with bilateral pelvic lymphadenectomy is recommended. Some authors have reported better survival for clinical stage I with primary radiotherapy (80%) than with surgery alone (56%) [33]. In younger women planned for radiation treatment, laparotomy or laparoscopy can be performed for the preservation of ovaries, surgical staging, and even removal of enlarged lymph nodes. Lesions in the distal portion of the vagina can be resected with partial vaginectomy combined with vulvectomy and dissection of inguinal lymph nodes (with survival rates ranging from 75 to 100%) [34]. Surgery for patients with advanced disease (stage IV) is usually exenterative, most often used in those with rectal or vesicovaginal fistulas, or those relapsing after radiotherapy. This intervention involves removal of a portion or the whole vagina. A very small number of series used only surgery for treating vaginal carcinoma [17]. Most centers prefer to use radiation treatment, since they can provide preservation of the vagina, although with very limited function [35].

Surgical treatment of vaginal carcinoma disrupts anatomic structures and relations, leads to loss of the vaginal function and produces significant morbidity, with immediate (operative) and late (postoperative) complications in adjacent organs (bladder, urethra, rectum). In addition to these immediate and late complications, radical surgery for vaginal carcinoma is associated with its own specific complications such as bladder dysfunction with hypertonia or atonia, with urine retention and urinary tract infections, ureterovaginal and vesicovaginal fistulas, and also with thrombosis of pelvic veins with edema of the lower extremities. Some authors have reported satisfactory results in clinical stage IV disease

with radiotherapy followed by the anterior or total exenteration of pelvic organs [36]. Vaginal reconstruction is usually recommended for sexually active patients.

Radiotherapy

The therapeutic and cosmetic effects of radiation for vaginal cancer are mostly satisfactory, making this treatment approach superior to surgery. It is thought that radiotherapy can preserve the anatomy and function of the vagina, especially in patients with early disease. Patients with advanced disease will have compromised anatomy and function as a consequence of their disease, regardless of treatment specificity.

Radiotherapy of vaginal carcinoma has to be individually planned. The treatment planning involves radiation of the primary tumor and pelvic or inguinal lymph nodes, depending on the tumor site in the vagina. Radiotherapy involves both transcutaneous radiation of the small pelvis and brachytherapy, which can be combined. Transcutaneous radiotherapy is applied before brachytherapy in order to reduce tumor volume and to increase the effectiveness of brachytherapy. Primary tumors in the vaginal fornix and introitus should be marked with radiopaque markers with CT support. Total dose of 50 Gy in 1.8-2 Gy daily fractions is usually administered; less than 50 Gy doses are not effective. Brachytherapy delivers a tumor dose of at least 70-75 Gy after transcutaneous radiotherapy (taking care that the total dose at the posterior bladder wall does not exceed 70 Gy and that the anterior rectal wall should receive no more than 60-65 Gy). High dose rate (HDR) brachytherapy is as effective and safe as low dose rate approach. Brachytherapy should be individually planned and depends on the disease stage [37].

Complications after radiotherapy of the vaginal carcinoma are identical to other malignancies of the female genitals. Acute complications are usually inflammations of the vaginal mucosa, urethra, rectum and bladder, treated symptomatically, and rarely requiring interruptions or delays of radiation treatment. Vaginal stenosis is the most common late complication. Gynecologic examination is more difficult in such cases, so special care should be taken not to overlook possible local relapses [38].

Chemotherapy

The experience with chemotherapy in PCV is limited due to the rarity of this disease. Chemotherapy has mostly been used as palliative treatment. However, recent reports suggest that chemotherapy given concurrently with radiation therapy (chemoradiation) yields superior survival in advanced stages (II-IV) of PCV [39-41], in agreement with the experience of cervical carcinoma [42,43]. Chemotherapeutic agents used in the combined treatment modality of vaginal carcinoma include cisplatin, 5-fluorouracil or mitomycin-C. Neoadjuvant chemotherapy with cisplatin and epirubicin to patients with advanced or recurrent squamous cell carcinoma and adenocarcinoma of the vagina has been described, but the results have been rather poor [44,45].

Conclusions

PCV is a rare gynecological cancer. This disease accounts for about 2% of all malignancies of the female genitalia. Most of the affected persons are over 60 years of age. Long-lasting HPV infection is the leading risk factor for PCV. The most common symptoms of the disease are increased vaginal secretion, bleeding, and dyspareunia. Diagnosis is made by way of histologic examination of every suspect vaginal lesion. Disease staging is solely clinical, except stage IV. The most important prognostic factors in PCV are disease stage, histologic tumor differentiation, lymph node status, and age at the time of diagnosis. The treatment of PCV is not clearly defined and it should be conducted in specialized institutions. There is no consensus regarding PCV treatment and individualized treatment approach is usually implemented. *In situ* lesions and early vaginal carcinoma can be surgically managed. However, the standard approach to treatment is radiotherapy. For early-stage PCV radiotherapy should be chosen as a final treatment in order to preserve vaginal anatomy and function, and in more advanced disease it helps avoid exenterative surgery. We believe that the preservation of the vagina carries certain psychological advantages, regardless of its function. We may conclude from our experience that preservation of vaginal function after treatment of invasive carcinoma is rarely achieved. In general, excepting the earliest disease stages, the results of treatment of PCV are modest.

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