

## Clinical Characteristics, Management and Prognosis of Patients with Vaginal Primary Malignant Melanoma

Editorial

Androutsopoulos G\*, Decavalas G

Department of Obstetrics and Gynaecology, University of Patras, Medical School, Rion, Greece.

### \*Corresponding Author:

Georgios Androutsopoulos MD,  
Assistant Professor, Department of Obstetrics & Gynecology, University of Patras, Medical School, Rion 26504, Greece.

Tel: +306974088092

E-mail: androutsopoulos@upatras.gr

androutsopoulosgeorgios@hotmail.com

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Vaginal primary malignant melanoma (VPMM) is an extremely rare and highly aggressive tumor [1,2]. It accounts for less than 3% of all vaginal malignancies and 0.3-0.8% of all malignant melanomas [1-3]. It is the 2<sup>nd</sup> most common malignant melanoma of the female genital tract [4]. Until today, less than 300 cases of VPMM have been reported in the English literature [1,2,5,6].

The estimated annual incidence of VPMM is 0.026/100,000 women per year [2,3]. However between various racial or ethnic groups, there are no significant differences in VPMM annual incidence [3,7]. VPMM most commonly occurs in postmenopausal women [8-11]. The median age at diagnosis of VPMM, is 57 years [8-13].

Despite proposed theories, the precise pathogenesis of VPMM still remains unclear [14]. However, an attractive explanation is that VPMM arises from melanocytes located aberrantly in vaginal epithelium [14,15]. Those melanocytes are present in the basal layer of vaginal epithelium in 3% of healthy women [16]. According to this theory, active junctional changes is the initial stage in malignant melanoma development [17].

As VPMM located in areas not exposed to sunlight, it is obvious that ultraviolet radiation is not implicated in its pathogenesis [7].

Although VPMM may arise anywhere in the vagina, it most commonly occurs in the lower one third (34%) and the anterior (38%) vaginal wall [2,8,9,12,15,18,13]. VPMM lesions may be single or multiple, pigmented or nonpigmented [13,19]. Also, most of VP-

MMs are polypoid and ulcerated [14,19]. Moreover, the clinical appearance of nonpigmented VPMMs may be similar with vaginal epithelial tumors [14,19].

The most common symptoms and signs in patients with VPMM, are: vaginal bleeding (80%), vaginal discharge (25%), palpable vaginal mass (15%) and pain (10%) [5,6,8,9,11,12,14,20].

VPMM is a very aggressive tumor with a propensity of early spread and metastasis development [1,6,21,22]. The extensive vascular and lymphatic network of the vaginal mucosa, explains adequately the aggressive clinical behaviour of VPMM [8,10,20].

Most patients with VPMM, diagnosed with advanced stage disease [1,6,21,22]. More specifically, they have local recurrences in the pelvis and distant metastases in the lungs, liver, bones and brain [8,14]. However, many patients with distant metastasis have synchronous local recurrence in the pelvis [8].

The most common histologic cell type of VPMM, is: epithelioid (55%) [10,14,19]. Other less common histologic cell types of VPMM, are: spindle (17%) and mixed (28%) [10,14,19].

FIGO staging system for vaginal cancer does not incorporate tumor size and regional lymph node status and it is inappropriate for VPMM staging [2,12].

Although there are various treatment options, it has not defined yet an appropriate and effective treatment protocol for patients with VPMM [10,23].

Surgery is the baseline treatment in patients with VPMM [2,10,23,24]. The spectrum of surgical operation varies from conservative (wide local excision) to radical (vaginectomy, pelvic exenteration) [2,10,20]. In patients that wide local excision with clear margins is possible, the role of radical surgery remains unjustified [2,10,23,25]. However in highly selected patients that wide local excision is impossible, pelvic exenteration may be reasonable [2,13].

Lymph node dissection is not recommended in patients with VPMM, because the rate of lymph node metastasis is low [10]. Although lymph node dissection has no survival benefits for patients with VPMM, it leads to significant morbidity [10,23,26].

Moreover the role of elective lymph node sampling in patients with VPMM, remains controversial [2,10,23,24]. Recent years, sentinel lymph node biopsy has gained popularity [10,24,27].

Radiotherapy in patients with VPMM includes vaginal brachytherapy and external pelvic radiotherapy [2,10,28,29].

External pelvic radiotherapy is used as primary treatment for patients who are unable or unwilling to have surgery [2,10,28,29]. Also it is used as preoperative treatment, to reduce tumor size and enable a more conservative surgery [2,10,25,28,29]. Moreover it is used as postoperative adjuvant treatment for patients with tumor size  $\geq 3$  cm, incomplete tumor resection or pelvic metastases [2,10,11,23,28,29]. However, although external pelvic radiotherapy reduces the risk of local recurrences, it has no impact on overall survival [13,23,24].

Especially in elderly patients with bad performance status and relevant comorbidities, we prefer postoperative vaginal brachytherapy [5,11,30,31]. It is well tolerated and reduces the risk of local recurrences [13]. Moreover, it is associated with less side effects and better quality of life, compared with external pelvic radiotherapy [5,11,31].

The role of postoperative adjuvant chemotherapy in patients with advanced stage VPMM, remains controversial [32]. Postoperative adjuvant chemotherapy achieve only modest response rates and has no impact on overall survival [25].

Postoperative adjuvant immunotherapy with interferon (IFN) or interleukin-2 (IL-2), confers survival benefits in patients with VPMM at high risk for recurrence. [6,22,24,33-35]. Moreover, the combined use of IFN and IL-2 is superior to the single use of IL-2 [36]. However, the toxicity of immunotherapy is significant [6,22,33,34]. Moreover, IFN associated with the generation of autoantibodies and the induction of autoimmune disorders [37].

The role of combined use of chemotherapy and immunotherapy (biochemotherapy) in patients with advanced stage VPMM has not been established [38]. Moreover, the toxicity of biochemotherapy is significant [24,34].

Patients with VPMM have poor prognosis [35]. As most cases with VPMM diagnosed at advanced stage disease, the prognosis is very poor despite treatment modality [1,6,11,22].

Prognostic factors for patients with VPMM, are: tumor size, tumor growth, lymph node status and treatment method [8,12,23,35]. Among them, tumor size (<3 cm) is the most important prognostic factor [8,12,24]. Tumor thickness is only a weak predictor of survival, in patients with VPMM [8].

The 5-year overall survival of patients with VPMM is 8.4-32.3% [1,8,10,13,15,24,35]. Moreover the prognosis of VPMM is much more unfavourable, compared with other vaginal malignancies and cutaneous malignant melanoma [14].

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