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Primary Malignant Melanoma of the Vagina in Bangladesh: Report of a Case Series and Review of the Literature

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Abstract

Objective: This study describes the characteristics of patients with primary malignant melanoma of the vagina and their treatment at National Institute of Cancer Research and Hospital in Dhaka, Bangladesh, from February 2013-January 2015. Materials/Methods: Eight patients with primary malignant melanoma of the vagina were identified. Medical records were reviewed for demographic information, treatment, and outcomes. This investigation was approved by the Ethics Committee of the National Institute of Cancer Research and Hospital. Results: The median age was 48 years (range: 35 - 65 years) and most patients were premenopausal. Seven of the eight patients presented with International Federation of Gynecology and Obstetrics (FIGO) stage II. The five patients had disease confined mainly to the upper and middle thirds of the vagina. One patient was diagnosed with stage IV disease. In two patients, cervical metastases were present. Almost all patients received radiotherapy. Two patients with stage II disease developed local recurrences within eighteen months. The one patient with stage IV disease died ten months after diagnosis. Conclusion: Primary malignant melanomas of the vagina are uncommon, highly aggressive tumors that are associated with poor overall survival. Surgery is the mainstay of treatment. Nearly 80% of vaginal melanomas will recur. Overall 5-year survival ranges from 5% to 25%. The size of the tumor (>than 3 cm) and the presence of lymphadenopathy at diagnosis worsen the overall survival.

Keywords

Melanoma, Vaginal Cancer, Bangladesh

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1. Introduction

Primary malignant melanoma of vagina (PMMV) is an extremely rare and highly aggressive tumor, with fewer than 500 cases reported worldwide [1]. It accounts for 5% of all vaginal malignancies and represents 0.2% to 0.8% of all malignant melanomas [2]. The amelanotic variety is exceedingly rare, accounting only 2% of all vaginal melanomas [3]. The estimated incidence of PMMV is between 0.26 and 0.46/1,000,000 women per year [4] [5]. Unlike cutaneous melanomas secondary to sun-exposure, it is unknown whether the incidence of vaginal melanomas varies by geographic region. While there have been a few case reports, there have been no previous case series describing genital tract melanomas in Bangladesh or in South Asia in general [6]-[10].

The etiology of this rare malignancy is largely unknown. PMMV originates from the malignant transformation of melanocytes in the basal portion of vaginal mucosa. The somatic mutation profiles of mucosal melanomas show BRAF mutations, common in cutaneous melanomas, to be rare while *c-KIT* mutations representing mutations of a type III transmembrane receptor tyrosine kinase are more common[11]. Early hematogenous metastasis is common due to the thin vaginal wall and rich surrounding lymphatic and vascular plexus and leads to a propensity for PMMV to recur at distant sites. Prognosis is worse than that of cutaneous melanoma, vulvar melanoma and other vaginal malignancies [2] [4] [5] [12].

There are no uniform treatment guidelines at present. While surgery is the primary treatment for vaginal melanoma, a combined modality approach with radiation and immunotherapy may improve survival [1] [13]-[17]. Prognosis is very poor even with aggressive surgery and adjuvant therapy.

We report the first case series of vaginal melanomas from Bangladesh.

2. Methods

PMMV are included in this study from the period January 2013 to January 2015 at National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh. This investigation was approved by the Ethics Committee of the National Institute of Cancer Research and Hospital. For this review of eight patients, there were no indeterminate results, missing data, and data outliers.

Clinical characteristics were recorded including age, menopausal status and presenting symptoms. Tumor factors included tumor size, location and International Federation of Gynecology & Obstetrics (FIGO) stage [18]. Treatment data included type of surgery performed, lymph node status and use of adjuvant therapy. Mean follow-up of patients has been three years. Most patients underwent either wide local excision (WLE) (with a margin $\leq$ 2 cm) or radical excision. Radical excision involved a radical hysterectomy, vaginectomy, and inguinal-femoral and pelvic lymphadenectomy for cases where the tumor was located in the upper and middle third of vagina. Total or subtotal vaginectomy was performed for distal, lower vaginal lesions. Adjuvant therapy with radiation, and/or chemotherapy was given for all patients. External radiation was given using a cobalt machine with two-field technique to a dose of 55 Gy. Chemotherapy with cisplatin and 5-fluoro-uracil concurrently with radiation was given to two patients as part of their primary therapy.

3. Results

NICRH is a government supported 300-bed hospital, which treats an average of 1000 new gynecologic cancer patients per year. Eight patients diagnosed with PMMV were identified. Patient demographics, tumor characteristics and treatment information are described in **Table 1** and **Table 2**. The most frequent presenting symptoms were vaginal bleeding, followed by vaginal mass and vaginal discharge. Some patients had more than one symptom. The median age at diagnosis was 47.9 years (range, 35 - 65 years). Six out of eight (75%) of patients were premenopausal. Four (50%) patients had multifocal disease and three (37.5%) had unifocal lesions. Five of eight patients (62.5%) had disease confined to upper and middle third of vagina. One patient had disease confined to the lower vagina (**Figure 1**—informed consent was obtained from each patient to publish the pictures). Seven patients (87.5%) had FIGO stage II cancers and one had stage IV malignancy based on direct invasion of the bladder. For two patients with stage II disease, metastases to the cervix were present. Seven patients underwent surgery and among them, four were treated by radical hysterectomy with vaginectomy and bilateral inguino-femoral and pelvic lymphadenectomy while three had wide local excisions of the vaginal tumors. A pelvic exenteration was recommended to the one patient with stage IV disease but she declined and received chemo-radiation. Adjuvant radiation was given to seven patients. Two patients received brachytherapy along with external beam radiation. Pelvic lymph nodes were involved in one of the four patients who underwent femoral

Table 1. Clinical and tumor characteristics in seven patients with primary vaginal melanoma.

Age	Number of Patients
<45	6
>45	2
Menopausal Status	
Premenopausal	6
Postmenopausal	2
Presenting Symptoms	
Vaginal bleeding	7
Vaginal mass	2
Vaginal discharge	3
FIGO Stage	
I	--
II	7
III	--
IV	1
Tumor Size	
<3 cm	3
>3 cm	5
Tumor Site	
Upper and middle third of vagina	5
Lower third of vagina	3
Lesion Number	
Multifocal	4
Unifocal	4
Pathology	
Melanotic	6
Amelanotic	2
Lymph node Status	
Positive	1
Negative	4
Unknown	3

Table 2. Treatment characteristics in seven patients with primary vaginal melanoma.

Surgical Intervention	Number of Patients
Wide local excision	3
Radical hysterectomy Vaginectomy Inguinal Pelvic lymphadenectomy	4
No surgery	1
Radiation Therapy	
Surgery with EBRT	4
Surgery with EBRT and ICRT	2
Surgery, chemotherapy and EBRT	1
Chemotherapy	
Chemotherapy, surgery, EBRT	1
Chemotherapy with EBRT	1

EBRT: external beam radiotherapy; ICRT: intracavitary radiotherapy.

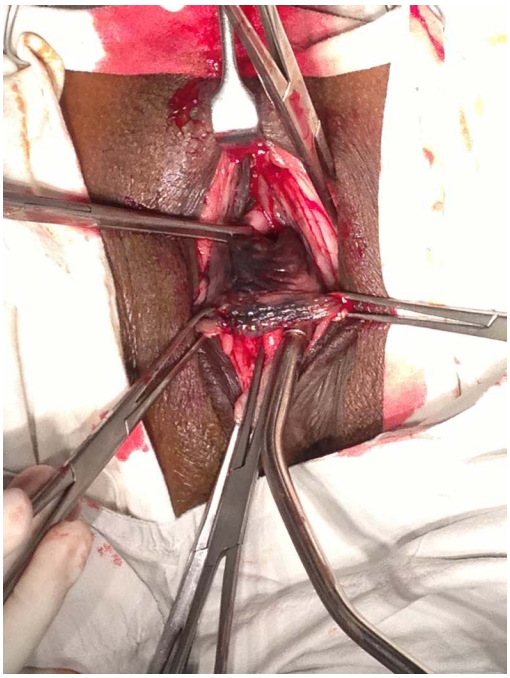
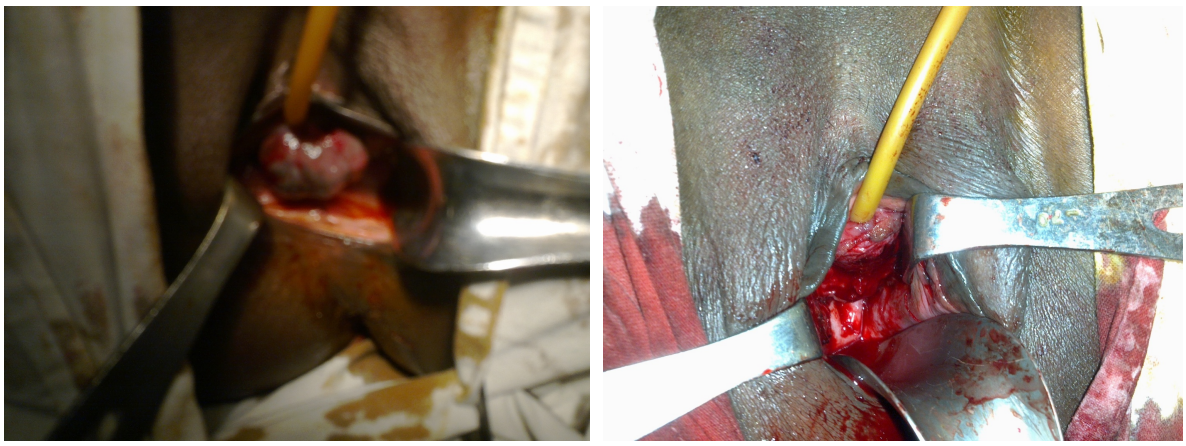


Figure 1. Stage II vaginal melanoma of the distal third of the vagina in the posterior vagina.



(a) (b)

Figure 2. (a) Stage II vaginal melanoma of the distal third of the vagina in the periurethral region; (b) stage II vaginal melanoma of the distal third of the vagina: After wide local excision.

and pelvic lymphadenectomy. Lymphedema developed in the four patients who underwent lymphadenectomy.

On follow-up, two patients with stage II disease (one with positive lymph nodes and one with negative nodes) had recurrences in the pelvis. One patient, age 45 years, underwent a wide local excision followed by external and intracavitary radiation (**Figure 2**—informed consent was obtained from each patient to publish the pictures). The second patient, age 40 years, underwent a radical hysterectomy, bilateral inguinal-femoral and pelvic lymphadenectomy followed by external radiation. Both patients experienced vaginal recurrences within 18 months of therapy and are currently undergoing chemotherapy with cisplatin. The one patient with stage IV PMMV had progression of her cancer and died within one year of diagnosis. This patient, age 35 years, presented during the first trimester of pregnancy with a 7 cm vaginal mass with direct extension into the bladder (**Figure 3**—informed consent was obtained from each patient to publish the pictures). She declined a pelvic exenteration. After a pregnancy termination, she received chemotherapy and external beam radiation but rapidly recurred both locally and distantly. She died 10 months after diagnosis.

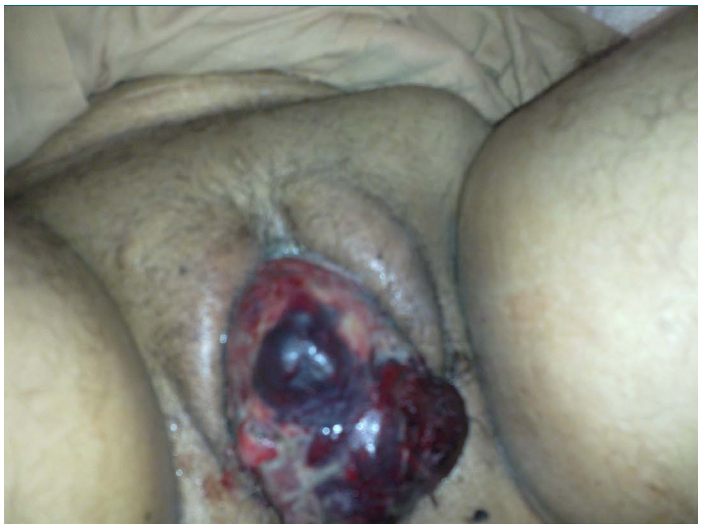


Figure 3. Stage IV vaginal melanoma with tumor prolapsing out of vagina with bilateral inguinal lymphadenopathy.

4. Discussion

We report on eight cases of vaginal melanoma seen in a two-year period at NICRH in Bangladesh. Bangladesh, a country of 166 million people, does not have a uniform cancer reporting system [19]. There are no national tumor registries and data collection and follow-up at individual hospitals is marginal so the true incidence and outcomes of cancers are unknown. While cervical cancer has been the most common gynecologic cancer in Bangladesh with at least 30 cases per 100,000 women, there is little information about other cancers of the lower genital tract [20]. A recent report detailed the first case series of squamous cell cancers of the vulvar seen at NICRH [21]. NICRH, a tertiary care, government hospital of 300 beds, is one of the few public hospitals devoted to the care of people with cancer in Bangladesh [22]. The need for cancer care in Bangladesh far outstrips the resources of this and other hospitals that provide oncologic services. At NICRH, there are currently four linear accelerators, two cobalt machines, and one brachytherapy machine that treat on average 400 cancer patients per day. As a consequence of wait times for radiation of 30 to 60 days, surgical interventions are considered whenever possible.

There is a growing literature of single-institution case reports and case series for PMMV around the world. Reports representative of the international experience with PVVM from the last 20 years are summarized in **Table 3** and **Table 4** [6]-[10] [16] [17] [23]-[57]. Of note, large series of patients with PMMV have required many decades of institutional experience [17] [29] [31]-[33] [35] [36] [38]-[47] [49] [54] [55] [58]. Overall, there do not seem to be geographic or ethnic variations in the clinical features of PMMV, or in the overall survival rates. From the surveillance, epidemiology, and end results (SEER) database in the United States from 1992 to 2005, 125 vaginal melanomas were identified [4]. In combination with vulva melanomas, the age adjusted incidence rates ranged from 0.87 in African Americans to 1.03 in Asians to 1.9 in non-Hispanic whites. In another SEER analysis of 201 patients with vaginal melanoma treated from 1988 to 2008, the population was 73% white, 11% black, and 16% Asian/American Indian [59]. Staging results showed 46% FIGO stage I, 18% stage II, 3% stage III, and 3% stage IV. A third SEER analysis compared the combined data from 762 patients with vulvar and vaginal melanomas to 55,485 patients with cutaneous melanomas from 1973 to 2008 [60]. In a multivariate analysis, age, stage, and positive lymph node status were independent negative prognostic factors for vulvar and vaginal melanomas whereas age, race, stage, radiation therapy, and lymph node status impacted survival negatively for cutaneous melanomas. The average age at diagnosis is in the sixth and seventh decades of life. The majority of women presented to medical attention with vaginal bleeding. The majority of vaginal melanomas are located in the lower third of the vagina [33] [55] [59]. In our patient series, the average age of 47 years was younger than other reports and the majority of our patients presented with upper vaginal masses.

Reviews of the largest case-series help to give a general picture of patient characteristics, therapeutic interventions, and outcomes. Forty-four patients over a 9-year period seen at Fudan University in Shanghai were treated with excisional surgery. Progression-free survival was dependent on depth of invasion, lymph nodes sta-

Table 3. Case reports of primary malignant melanoma of the vagina.

Country	Year	Age	FIGO	Treatment	Follow-Up (Months)	Outcome
Japan [53]	2015	59	II	RH, V, DTIC, IM	5	Lung metastases
Bulgaria [23]	2014	71	II	RH, V, LN IM, DTIC	21	Died 21 months
China [31]	2014	35	II	RH, LN, V	6	Pelvic recurrence; lost to follow-up
Denmark [54]	2013	77	II	exenteration	7	Recurrence at 7 months
Morrocco [51]	2013	70	IV	imatinib	18	regression
India [7]	2013	60	II	WLE, EBRT CT: TEM	12	Alive at one year
Greece [24]	2013	80	II	WLE, ICRT	5	Died lung metastases at one year*
Germany [55]	2012	44	III	exenteration	4	Died at 4 months
India [10]	2012	66	II	WLE,EBRT	12	Died with widespread recurrence
China [56]	2011	54	III	RH, V EBRT, IM, CT	12	Brain metastasis
India [6]	2009	60	II	WLE DTIC	12	Alive one year
Turkey [25]	2009	51	!	V, LN DTIC, cispltin	21	Nodal metastases at 9 months Alive at 21 months
Bangladesh [9]	2008	52	I	WLE, EBRT	--	Lost to follow-up
Nepal [8]	2007	60	II	WLE, EBRT	6	Recurrence 3 months Died at 6 months
Germany [26]	2007	58	I	WLE, EBRT	6	Metastasized at 6 months
Spain [27]	2004	40	I	RH, V, LN EBRT, IM	8	Recurred in liver and ascites at 7 months Died at 8 months
South Africa [28]	2004	49	II	WLE, IM DTIC & carboplatin	24	Alive at 2 years
Israel [29]	2002	67	II	WLE, EBRT ICRT	11	Alive at 11 months
Italy [15]	1998	45	IV	Exenteration DTIC fotemustine	12	Metastases at 4 months Alive at 12 months
USA [30]	1998	55	I	WLE, LN	13 years	Alive at 13 years

CT chemotherapy; DTIC dacarbazine chemotherapy; EBRT: external beam radiotherapy; ICRT: intracavitary radiotherapy; LN lymphadenectomy; RH radical hysterectomy; TEM: temozolamide chemotherapy; V vaginectomy; WLE: wide local excision; *personal communication with authors.

Table 4. Case series of primary malignant melanoma of the vagina.

Country	Dates of Care	# of Patients	Treatment	Recurrence and Survival
Bangladesh	2013-2015	8	4 RH V LN 3 WLE	43% recurrence; 14% died in two years
China [32]	2002-2011	44	21 WLE 20 RH V 5 EBRT,30 IM, 11 CT	68.2% recurred; 47.7% died 5 lived longer than 5 years
France [52]	2000-2010	6	WLE	Median progression free survival 10.5 months
USA [67]	1993-2012	14	5 WLE 3 WLE, LN 3 radical excision 3 exenteration 2 preop CT, 1 EBRT	Recurrence in 10 of 14 patients Median time to recurrence 6 months Median overall survival 2.1 years
France [58] 12 institutions	1990-2007	46	4 exenteration 19 WLE 7 V 9 RH V LN 5 EBRT, 6 ICRT 6 CT, 4 IM	Median relapse free survival 10.9 months Median overall survival 28.4 months

Continued

USA [30]	1980-2009	37	28 WLE 5 exenteration 5 EBRT, CT	Progression-free survival: 11.4 months, Overall survival: 19 months.
USA [57]	1970-2009	15	WLE, EBRT, CT, IM	2/15 alive over 8 years follow-up
China [34]	1970-2005	31	15 Surgery & IM 7 surgery 4 CT & IM 3 CT 2 no treatment	35.5% recurrence; 32.3% 5 year survival
USA [35]	1976-1986	5	5 WLE 3 CT, IM	Time to recurrence 7 months; mean survival 31 months
USA [36]	1970-2002	26	7 exenteration 10 WLE 3 RH V; 1 V 3 EBRT only	Fifteen patients died of the disease (3 - 83 months) Four patients no evidence of disease (5 - 24 months) Four patients alive with disease (6 - 276 months)
USA [37]	1977-2001	35	10 WLE 2 V 10 RH V 2 exenteration 11 EBRT, 26 IM or CT	Median survival 20 months Surgical therapy: median survival 25 months Radiation therapy: median survival 13 months
United Kingdom [50]	1975-2000	9	2 EBRT 1 RH,V 6 WLE	Median survival 24 months (range 4 to 60 months)
China [16]	1979-1997	9	9 surgery, CT, IM	20% 5-year survival; one long term survivor at 19 years
USA [38]	1990	10	10 surgery, EBRT, CT	Mean time to recurrence: 8 months Mean survival: 15 months
Austria [39]	1982-1996	14	7 biopsy 5 WLE 1 RH V 1 exenteration	Mean survival 10 months (range 1 - 153) 21% 5-year survival
USA [40]	1966-1996	7	2 WLE 2 WLE, EBRT 2 ICRT 1 exenteration	Median time to death 20 months (2 ot 48 months) All Dead of disease
USA [41]	1982-1996	13	5 V 9 WLE	64% Estimated 5-year survival
USA [42]	1972-1992	8	4 conservative: WLE, CT, EBRT 4 Radical: exent, RH	4 patients radical surgery: 75% 2-year survival 4 patients conservative surgery: 0% 2-year survival
Italy [43]	1969-1993	20	15 WLE	15 evaluable patients; 2 died postoperatively All patients died of disease; median survival 19 months
USA [44]	1986-1992	4	4 exenteration	All underwent pelvic exenteration; One post operative death Three patients alive at 31-to 97 months
Hong Kong [45]	1978-1990	10	1 exenteration, CT 2 RH V 3 WLE 3EBRT ± CT	Five patients died 2 - 22 months Five patients median survival 18 months
USA [46]	1936-1988	15	3 WLE 2 RH V 5 V, vulvectomy 3 exenteration 2 EBRT	17.4% 5-year survival Two patients survival more than 5 years
Spain [47]	1984, 1986	2	1 RH V 1 EBRT	Died at 4 and 6 months
Sweden [48]	1960-1984	26	Not stated	13% 5-year survival
USA [49]	1935-1976	19	7 RH V 8 WLE, EBRT 4 EBRT, ICRT	21% 5-year survival One long-term survivor at 14 years

CT chemotherapy; EBRT: external beam radiotherapy; ICRT: intracavitary radiotherapy; IM: immunotherapy; LN lymphadenectomy; RH radical hysterectomy; V vaginectomy; WLE: wide local excision.

tus and the addition of postoperative radiotherapy [38]. In another series over a 35-year interval in Guangzhou, China, survival of the 8 out of 31 patients correlated both with smaller tumor size and the addition of immunotherapy [35]. In this small cohort, the five-year survival rates of women who received surgery plus interferon immunotherapy versus surgery alone was 47% and 29% respectively. For 37 cases of vaginal melanoma identified over a 29-year period, treatment ranged from wide local or radical excision (76% of patients) to pelvic exenteration (14% of patients) [33]. Ten percent of patients received radiotherapy and/or chemotherapy. Eighty-nine percent of women recurred within two years. Recurrence was local in seven patients (22%), distant in 20 (63%), and both local and distant in five (15%). The most common sites of distant recurrence were lungs and liver. Median progression-free survival was 11.4 months, and median overall survival was 19 months [33].

One retrospective, multi-institution study collected information on 54 patients with PMMV from 12 institutions over a 17-year period [58]. Forty-six patients were treated with curative intent (**Table 4**) and 8 patients received palliative management. The FIGO stage breakdown was 70% stage I, 12.5% stage II, 15% stage III, and 2.5% stage IV. All 46 patients had *c-KIT* testing by immunohistochemistry, which was positive in 80.6% of pathologic specimens. While recurrence rates were higher for patients who had *c-KIT* mutations, by univariate analysis, positivity did not correlate with overall survival.

Overall, prognostic factors include tumor size, depth of invasion, mitotic counts, and lymph node involvement [38] [55]. Lesions less than 3 cm have better survival than lesions greater than 3 cm. Even though the majority of PMMV presenting at the early FIGO stages of I and II, 5-year survival rate ranges from 0% to 21%. The two-year survival rate for our patients is 86%. Our recurrence rates and survival over a 2-year period appear better than noted in other reports but our follow-up time is short.

In South Asia, there have been several case reports of PMMV [6]-[10]. Three cases have been reported from India, a 60-year-old menopausal woman with a 3 cm lesion in the lower vagina treated by excision and radiation, and a 36-year-old with a 7.5 cm lesion treated with WLE and chemotherapy, both disease-free at one year and a 66-year-old who died within a year after WLE and radiation [6]-[8]. A case report from Nepal describes a 60-year-old with a 7 cm lesion treated with WLE, radiation, and chemotherapy, who died from widespread metastases within six months [9]. In 2008, the first case of vaginal melanoma was reported in Bangladesh [10]. The patient was a 52-year-old postmenopausal woman with a 4 cm lesion in the lower vagina treated by surgical excision followed by radiotherapy. The paucity of prior reports from South Asia may reflect the challenges of data collection and follow-up in this resource-limited region. Our two-year experience of eight patients suggests an under-reported incidence of PMMV.

Existing literature has detailed the treatment options of surgical excision, and radiation [1]. There are scattered reports on both chemotherapy and immunotherapy [27] [35]. The radical nature and extent of surgery and the addition of adjuvant therapy may influence the prognosis but reports are mixed [41] [42] [47]. Surgery may be the only potentially curative treatment for local disease. Surgical management ranges from either by wide local excision (WLE) to a more radical approach including full vaginectomy or pelvic exenteration. Radical surgery has been promoted as the preferred approach to reduce local recurrence and improve survival [41] [47] [49]. Recent reports have argued that WLE can achieve equivalent survival rates to more radical resections [29] [31] [33] [36] [39] [42] [44] [45] [61]. There was no correlation between type of surgery and survival greater than five years in one case review of 21 long-term survivors [55]. In a series of 85 patients with all types of lower genital tract melanomas including 15 PMMV, survival for those who could not undergo surgery was significantly worse than for those where WLE was possible [57]. However, treatment should still be individualized based on the size and location of disease. If local excision is impossible because of inability to get free margins, radical surgery may be reasonable to completely remove the visible tumor. Four of our patients underwent radical excision and three underwent wide local excisions based on the locations and the size of the tumors. Role of lymphadenectomy is controversial [1] [33] [39] [41] [62]. Recent studies have argued that lymphadenectomy is not therapeutic and carries significant morbidity [33] [36] [39] [61]. All of our patients who underwent lymphadenectomy developed lymphedema. Lymph node status may have a prognostic significance and as better therapies are developed, this may be important for treatment planning [33]. Sentinel lymph node biopsy to confirm node status has replaced full lymphadenectomy in the setting of radiological and clinically negative lymph nodes in vulvar melanoma. Due to its low morbidity, it has recently gained popularity in both cutaneous and vaginal melanoma [51] [62]-[64].

Radiation therapy has been routinely used as adjuvant therapy although there are no large series comparing surgery alone to surgery with radiation. A recent study of carbon ion radiotherapy for 23 patients with genital

mucosal melanoma showed a recurrence rate of 61% with a median follow-up of 17 months and a 53% three-year survival rate [65]. Seven of our eight patients underwent surgery with adjuvant radiotherapy, which is similar with other reports [1] [5]. Two patients are currently alive with vaginal recurrences and carry a very guarded prognosis. One patient with stage IV PMMV died within a year of diagnosis.

Since the first report of vaginal melanoma in 1887, there has been a slow accrual of case studies and case reports over the past 128 years [66]. PMMV are uncommon, highly aggressive tumors that are associated with poor overall survival. Based on case series, PMMV makes up between 2% to 11% of all primary vaginal cancers and less than 1% of all melanomas [12] [49] [55]. Nearly 80% of vaginal melanomas will recur. Current collective experience suggests that surgical excision followed by adjuvant therapy such as radiation and immunotherapy are the best therapeutic interventions available. Chemotherapy plays an unclear role, as data is extremely limited [67]. Tumor registries and outcome tracking will be important to fully define the incidence and behaviors of these rare tumors in resource-limited regions such as South Asia. In resource rich countries, *c-KIT* mutations should be tested and participation in clinical trials has been recommended [14].

Conflict of Interest

The authors have no disclosures

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