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Primary Malignant Melanoma of Vagina

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ABSTRACT

Objective(s): The present study was carried out to describe the clinicopathological correlation, treatment and to analyse the treatment outcome in patients with primary malignant melanoma of the vagina.

Methods: We retrospectively analysed five cases of primary malignant melanoma of vagina (MMV), which presented with vaginal bleeding and discharge and reviewed the world literature on mucosal melanoma. The survival analysis was carried out with Kaplan Meier Method, and survival was compared using Wilcoxan rank sum test.

Results: The tumors were predominantly located in lower vagina with a mean size of 4 x 3.5 cm. Two patients underwent posterior pelvic exenteration and pelvic lymph node dissection (PLND), two other had wide local excision, and one patient had no surgery. Adjuvant treatment with external beam radiotherapy was given in two patients; brachy therapy in two patients and one patient received chemotherapy. During the follow-up three patients had local failure, while two developed metastasis to lung and bone. Both the patients having tumour >3 cm, developed metastases; and metastasis was found to have a significant effect on survival. Disease free survival at six months was 40% (95% CI 5.2–75.3), which dropped to 20% (95% CI 0.8–58.2) at two years, all patients failed within 30 months.

Conclusions: High mortality despite radical surgery and adjuvant treatment suggests aggressive biological behaviour of disease. Optimal management of malignant melanoma of vagina requires early detection and multi-modality treatment with high fraction radiotherapy followed by vaginectomy.

Key words: Melanoma, vagina, mucosal melanoma, high fraction radiotherapy, pelvic exenteration

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INTRODUCTION

Malignant melanoma is a relatively common cutaneous malignancy in the Western world but is rare in Asian population, India is one of the low incidence regions (0.5%) of the world[1]. Cutaneous areas exposed to sunlight are most vulnerable, but rarely melanomas can occur on mucous membranes. Primary malignant mucosal melanomas (MMM) have been known to arise from mucous membrane of almost all the organ system. The incidence of MMS has ranged from 2 to 10% in various series[2–5], with majority of these lesions arising in the head and neck and vulval regions[2].

Malignant melanoma of vagina (MMV) is an exceedingly rare entity accounting for 0.4–0.8% of all melanomas,

2–5% of genital melanomas, and 2.6–2.8% of all primary malignant tumours of the vagina[6–8]. There have been less than 170 cases of vaginal melanomas reported in English literature[9–12]. These tumours are more aggressive than cutaneous melanomas with 5-year survival rates being 5 to 10%[13–15]. Among the primary vaginal tumours, vaginal melanomas have the worst prognosis[6,16].

MMV is primarily a disease of postmenopausal women, The bleeding is commonest presenting symptom and is invariably slight, the discharge when occurs is often blood tinged, foul smelling or purulent. Though malignant melanoma may occur anywhere in the vagina, it is commonly found in the anterior wall, and in the distal one-third of the vagina. It may be polypoidal, pedunculated, papillary or fungating in appearance. Pap smear and fine-needle aspiration cytology represents a valuable diagnostic tool in the evaluation of palpable lesions of the vagina with benefit of safety, simplicity, and accuracy (false-positive and false-negative rates are 0 and 4.6%, respectively)[17]. The diagnosis may pose a problem due to anatomical lack of awareness[18]. On fat-saturated T1-weighted magnetic resonance imaging, the vaginal lesions are demonstrated more clearly than by conventional T1- and T2-weighted images. Furthermore, the fat-saturated image is able to detect the bladder and rectal metastasis from the vaginal lesion[19,20].

The tumours are histologically divided into three types (1) epitheliod, (2) spindle cell or sarcomatoid, and (3) mixed. The tumours are frequently ulcerated and, when nonpigmented (10% are amelanotic) may be mistaken for epithelial tumours. In addition junctional activity or melanin pigment, which are helpful clues for diagnosis, are often obliterated by extensive ulceration, necrosis, and other tissue reactions. Immunohistochemical staining with S-100 protein complement diagnostic histopathology[21].

Due to extensive lymphatics of the vagina, and melanoma's propensity for the haematogenous spread, early metastases are common. The most frequent recurrence is local and distant site for metastasis is lung[13]. The treatment of vaginal melanomas varies and include individually or in combination; (1) conservative-wide local excision (WLE), (2) radical surgical extirpation, (3) radiotherapy, (4) chemotherapy, and (5) immunotherapy. Loco-regional relapse occurs in 60% of the cases emphasising the importance of local treatment[22].

Regardless of primary therapy, results of the treatment of vaginal melanomas have been uniformly poor[23]. The present report deals with the clinico-pathological review of 5 cases of primary MMV treated at our centre with a review of the literature.

PATIENTS AND METHOD

The electronic database of Regional Cancer Centre on Ingress® (Ingress Inc., USA) was searched, using ICD -O (2nd edition) code for site (C52.9) and the histopathology code for melanoma (M-8720/3). A total of 5 cases were identified between 1982 and 1997 (16 years). Cases with previous history of cutaneous melanoma were excluded. Pre-treatment evaluation and pathological review was performed at institution and diagnosis was confirmed in each case. Pigmentation, depth of invasion, vascular invasion, intraepithelial spread, frequency of mitosis and presence of junctional activities were measured whenever the material was adequate. Conservative treatment included radiotherapy, chemotherapy, WLE, or in combination of the above. Radical therapy included pelvic exenterative surgery, i.e. radical hysterectomy, total vaginectomy, and pelvic lymph node dissection (PLND). An analysis of pattern of failure was performed. All patients were observed for the follow-up time ranging from 4 to 30 months with a median of 7 months. Disease free survival rates were estimated using the Kaplan- Meier method[24] and compared using Wilcoxon rank-sum test.

RESULTS

Over 16-year periods, a total of 167 patients with melanomas were registered, of which 21 had malignant mucosal melanoma (MMM). These constituted 12.9% of total melanomas and 0.03% of all cases admitted during the same period. Of these 21 MMM, there are five cases of MMV. At the same time, about 309 cases of vaginal cancers were treated in the centre and MMV constituted 1.5% of all vaginal tumours. The age at presentation ranged from 34 to 62 years with mean age of 53.4 years. Only one patient was premenopausal. The most common presenting symptoms were vaginal bleeding and discharge (4 of 5 patients). Other presenting symptoms included vaginal mass and dyspareunia. The average duration between the onset of symptoms and subsequent presentation for medical evaluation ranged from 1–24 months with a mean of 10.4 months. The size of the lesions ranged from 2 to 7 cm in largest diameter with a mean size of 4 cm. In four patients, the lesion was single but one patient had multiple lesions. All the lesions were located in the distal one third of the vagina; however, two had tumour extension to the middle third of vagina. Two patients had lesion located on the anterolateral, two on the posterolateral wall while one had lesion on the anterior wall of the vagina. Haematological and biochemical tests were normal. Chest X-ray revealed pulmonary metastasis in one case. X-ray cervical spine in another case complaining of neck pain revealed lytic areas in

the C1–C2 vertebra with compression of the cord (Table 1).

Diagnosis of MMV was made histopathologically by demonstration of intracellular melanin (Figure 1) and was confirmed by Masson- Fontana staining. Immunohistochemical staining with S-100 protein, carried out on our more recent patients, showed diffuse and intense staining which confirmed the diagnosis. The majority of these tumours were highly cellular with extensive infiltration to submucosal compartments. They were mostly solid with cells arranged in sheets, nests, and fascicles. Cells were predominantly epitheliod or more rarely spindle shaped. All the tumours were high grade with a greater degree of anaplasia and mitotic activity. Both the patients undergoing radical surgery showed abundant melanin pigmentation and one of these had high junctional activity. Both these tumours were deeply infiltrating and vascular invasion was not present. An intraepithelial spread was seen in one case. Pathological lymph node status was not known in conservative group while in radical group both the patients had negative pelvic nodes. The cell types were epithelioid in one case, and mixed with epithelioid predominance in the other. Recurrence from one epitheliod tumour was found to be spindle cell later on. One tumour with bone metastasis showed very high mitotic activity of 25/10 HPF. A patient who had low initial counts, on recurrence showed high mitotic activity of 33/10 HPF.

As expected from patients collected over one and half decade, the treatment was very heterogenous. Radical surgery was carried out at our centre on two patients while two patients underwent WLE elsewhere. One patient (NF) did not have any surgical intervention due to metastasis to the lung at the time of presentation and was treated with palliative radiotherapy and decarbazine (DTIC).

One patient undergoing radical surgery had local recurrence at labia after 13 months and was salvaged with reexcision and adjuvant external radiotherapy; she is alive without disease at 20 months. Both patients undergoing conservative treatment failed locally after 5 and 28 months of initial treatment respectively. Recurrences were treated with DTIC and palliative radiotherapy. All the patients in the present series failed, failure was local in 60% and distant in rest.

The mean disease free survival time (DFS) was 9.4 months with a median of 5 months. This was 11 months in conservative group, while it was 7 months in radical group. The differences were not significant by Wilcoxon rank-sum test. DFS at 6 months was 40% (95% CI 5.2–75.3), which dropped to 20% (95% CI 0.8–58.2) at 2-year and all the patients failed by 30th month (Figure 2). Duration of symptoms correlated with size of the tumour and metastasis. Two patients having symptoms >4 months had tumour >3 cm and both developed metastasis. Patients with metastasis at presentation and tumour size greater than 3 cm had poor DFS compared to those with tumours less than 3 cm and metastasis (0% vs. 66.6% at one year; p=0.03). Both the patients undergoing radical treatment failed by 13th month, while DFS was 33% in patients undergoing conservative treatment, the difference was however not significant (p=0.7) (Figure 3).

TABLE 1

Details of the symptoms, treatment and follow-up among patients of vaginal melanoma treated at our centre

S.No	Age	symptoms (months)	Size (cm)	Initial treatment	DFS	Site failure	Treatment at failure	Overall survival (months) and status
1	55	24	7x7	Local RT 500cgy/wk x5, DTIC	0	Lung	–	6 with disease
2	62	1	3x2	Limited excision XRT& ICR; 50Gy/ 26f r+25Gy to vaginal surface	28	Local; Ascites	DTIC, Mitomycin	30 with disease
3	61	–	2x2	WLE vaginal sorbo 6600cGY	5	Local, anterior vagina	XRT vulva 3000cGY/10fr; 2 wk high dose	7 with disease
4	55	3	3x3	Posterior pelvic exenteration & PLND	13	Local, Labia	WLE RT 46Gy/23	20 without disease
5	34	12	5x4	Posterior pelvic exenteration & PLND	1	Bone	Single palliative RT to C2 spine 1000cGY & steroid	4 with disease

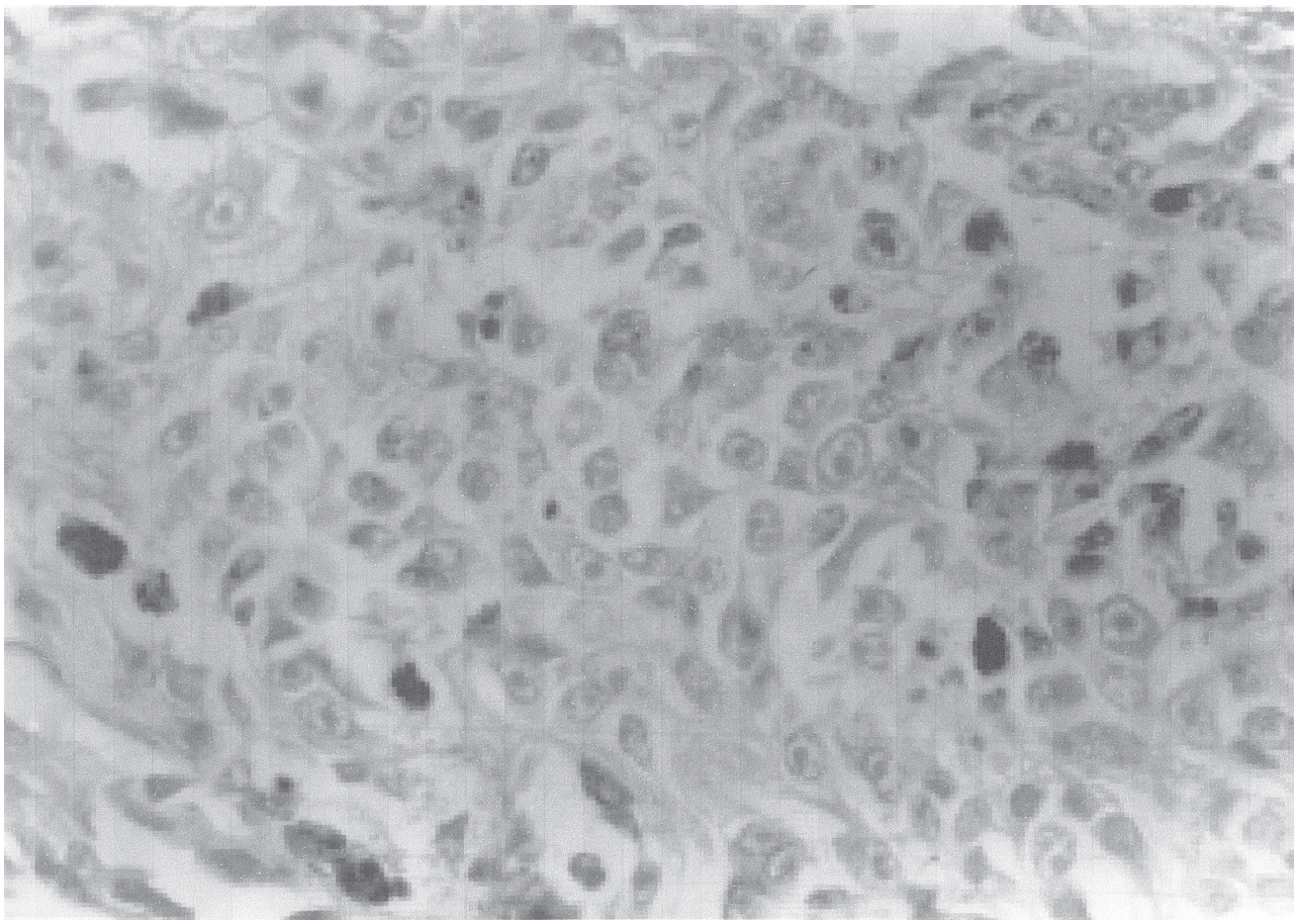

Fig. 1. Malignant melanoma-showing epithelioid malignant cells having vesicular nucleus, prominent nucleolus and scattered mitotic figures. Blakish melanin pigment is seen in some of the melanoma cells (H & E x400)

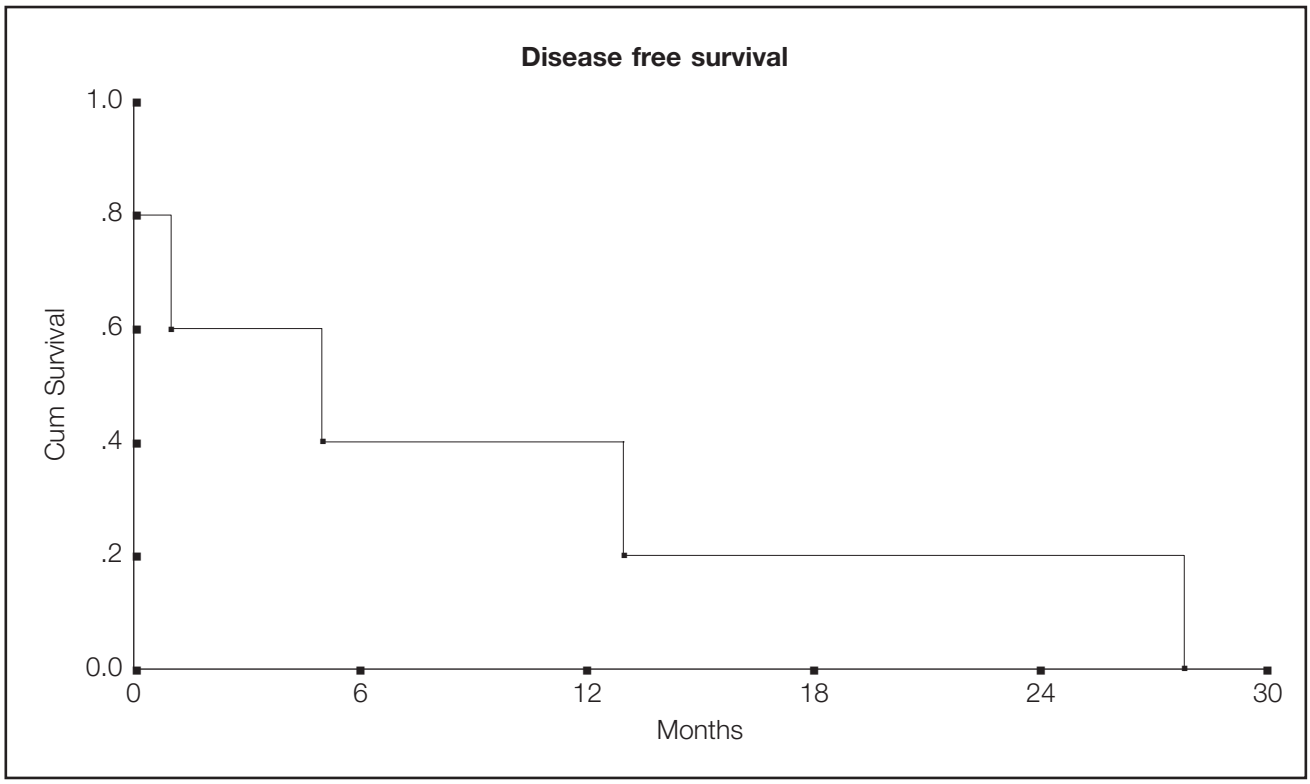

Fig. 2. Disease free survival in patients with malignant melanoma of the vagina

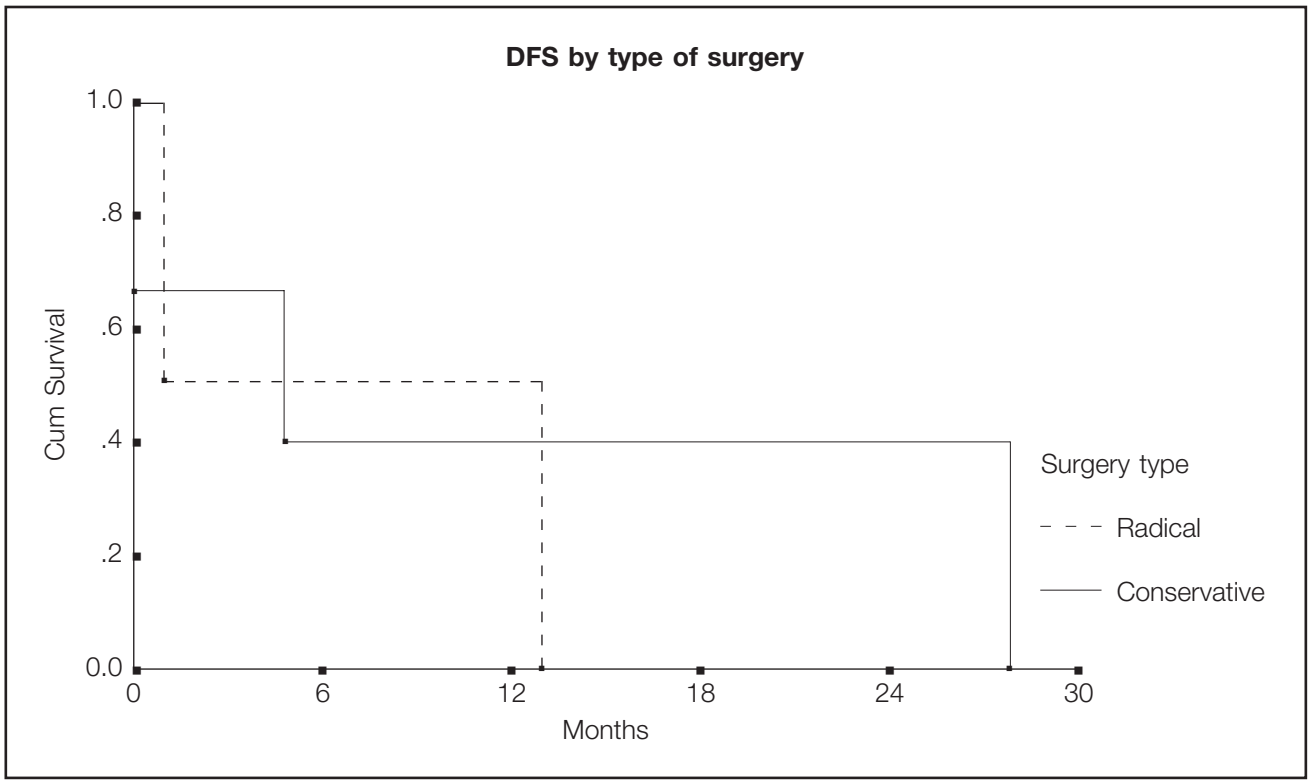

Fig. 3. Disease free survival in patients with malignant melanoma of the vagina by the type of surgery.

DISCUSSION

Primary MMV arises from melanocytes, which may be present in the epithelium of the vagina[25] or may arise from clinically recognizable nevi[26]. Melanocytes are embryologically derived from the neural crest cells and are found in the basal portion of the vaginal epidermis in 3% of normal adult females. It is believed that during the migration of melanocytes from the neural crest to the epidermis some come to rest aberrantly in the vaginal mucosa; it is from these ectopic sites of melanocytes that vaginal melanoma is thought to arise. Melanocytes are primarily an integumental component; hence it is not surprising to see MMV frequently near the mucocuteneous junction. The possibility that the mucosal lesion is in fact a metastasis arising from a primary cutaneous melanoma must be considered in every case, and a careful search for skin lesion should be carried out in addition to the workup for metastasis.

Pigmented nevi, and melanotic macules are lesions that simulate mucosal melanomas but are not associated with a poor prognosis. Generally, they occur in adults as a single, acquired, intensely pigmented lesion, although familial and multiple nevi have also been reported[27]. Pigmentation (melanosis, melanoplakia) precedes melanoma in about one third of patients[28,29]. This pigmentation is physiological in many coloured races and represents a negligible risk of malignant transformation[30]. In general, melanoplakia with increasing clear cells in the epithelium, S- 100 protein positive cells, and large number of melanophages in deep portion of the lamina propria, are at risk of malignant transformation[31].

The origin of melanocytes in the vagina is uncertain. Melanocytes arise in the neural crest and migrate through the mesenchyme to come to rest in the epidermis[25,32]. It is believed that during this migration, melanocytes come to rest in the vagina. Melanocytes are present in the vaginas of 3% of normal women[32]. Vaginal melanoma is believed to arise from these ectopic sites of melanocytes. Lateral junctional spread is seen in the majority of the primary mucosal melanomas[6,33].

Although tumour thickness is a strong prognostic variable for survival in cutaneous melanoma, tumour thickness in vaginal melanoma was shown to affect only disease-free interval, with lesions of 6 mm or less associated with a longer interval.

The apparent lack of demonstrated significance for survival in vaginal melanoma may result from the advanced depths of penetration at the time of diagnosis. In a large series of 1110 patients with cutaneous melanoma, 25% of the lesions were less than 0.76 mm at the time of diagnosis, with an associated 92% 5-year survival[35]. Breslow[34] reported

an 80% 5-year disease-free interval when tumour thickness was less than 2.25 mm. In contrast, the minimum tumour thickness noted as reported in a series of 15 patients was 3.0 mm[34]. Among 31 patients for whom tumour thickness was reported in the literature, the range of measurable thickness was 1.0 mm to greater 20 mm, with a mean of 6.34 mm and median of 5.0 mm. There were only four patients reported to have tumour thickness less than 2 mm[6,36]. Thus, if vaginal melanoma patients could be diagnosed with decreased tumour thickness, perhaps survival would improve and tumour thickness would become significant for survival. Vaginal melanoma, like cutaneous melanoma can recur long after 5 years. Once a recurrence is noted, prognosis is extremely poor, with a mean time from recurrence to death of only 8.5 months. Several forms of salvage therapy for recurrent vaginal melanoma have been attempted. Chemotherapy seems to play a very limited role in vaginal melanoma treatment, with no marked response demonstrated[37,38].

Radiation therapy for recurrence or primary treatment can also be considered. Although melanomas were generally regarded as radioresistant tumours, four of the 13 vaginal melanoma 5-year survivors were treated with radiation therapy[6,39]. Doses and method of radiation varied, but most of these patients were treated by combination external and brachytherapy. Recent reports of cutaneous melanoma have indicated that the use of high-dose fractions (greater than 400 cGy) yielded a better response rate than did conventional or low-dose fractions[40]. Harwood and Cumming[53], at Princess Margaret Hospital, treated mucosal melanomas of the head and neck with irradiation fractions greater than 400 cGy, and obtained an 85% complete remission rate, compared with only a 28% complete remission rate with smaller fractions. These authors also treated four vaginal melanoma patients and obtained a complete response in all, although two recurred within 28 months. Harrison et al[39] obtained good local control in three vaginal melanomas using high-dose fractions, with one long-term survivor. Further follow-up of patients treated with high-dose fractions in this manner is needed to ascertain whether this method will significantly improve local control and, more important, survival.

The average age at presentation of MMV is in the 6th and 7th decade of the life. Age at presentation has not been found to affect survival[17,41]. Three cases are reported in third trimester of pregnancy. Prognosis reportedly worsens during pregnancy as pregnancy increases the secretion of Melanocyte-Stimulating Hormone (MSH)[42].

Prognostic factors influencing survival in cutaneous melanomas like tumour thickness, anatomical location, stage, level of invasion and initial operative management are probably not applicable to MMV[15,43]. Vulvar melanomas, on the other hand, have been shown to behave like cutaneous melanomas with a fair to good survival even without radical therapy (40%, 5-year survival)[44,45]. The extremely poor prognosis of vaginal melanomas is not clearly understood. Possible reasons for poor survival include: (i) non-specific symptoms resulting in late presentation; (ii) The layer of submucosal connective tissue are poorly defined and skin appendages are absent which leads to early spread of local disease; (iii) multifocal nature, histologically and anatomically advanced disease; (iv) anatomical constraints precluding surgery with generous margins and consequently resulting in a high incidence of local recurrence; and (v) rich vascularity and multiple lymphatic drainage pathways may mean a predisposition for early dissemination.

Reid et al[11] from complied data on 115 patients showed that patients with vaginal lesion <3 cm in greatest diameter experienced significantly better survival than those with lesion >3 cm. They also found tumour thickness to be a significant prognostic variable for disease free interval but not for overall survival, though it did appear to have a favourable outcome when the tumour thickness was <2 mm[11]. DeMatos et al[46] suggested that tumour ulceration and thickness of the primary lesion has a measurable impact on prognosis, whereas the presence of regional metastases at presentation did not. Others have, however, shown that depth of invasion, vascular invasion, and smaller lesions has no survival advantage[12,41]. Regardless of the extent of primary surgery, positive histological margin or the presence of melanoma in situ at the edge of the specimen results in higher incidence of local failure and poor survival rates[10].

Borazjani et al[41] correlated length of survival with mitotic counts, a mean survival time of 21 months was observed for mitotic count of 6 or less per 10 HPF vs. 7 months for mitotic count of greater then 6 per 10 HPF. They also suggested that vascular invasion may indicate a poor prognosis, but its absence does not predict better survival. Liu et al[47] reported that survival time differed significantly in patients with and without pelvic lymph node metastasis (7 vs. 41 months) and in patients with and without vascular tumour thrombi (13 vs. 43 months), however, mitotic index of tumour cells and lymphocytic infiltration were found to be of no prognostic value. This is contrary to mucosal melanoma of the head and neck where the presence of regional lymph node metastasis does not seems to affect the prognosis[48,49].

Treatment failure due to regional node metastasis alone is rare[3]. Cantuaria et al[50] advocated

lymphadenectomy only for grossly positive nodes. Both patients undergoing PLND in our series were found to be node negative on histopathology. Similarly, none of the patients in this series failed regionally. This difference in pattern of spread may be due to the absence of lymphocytic infiltration among our patients, suggesting low or no host immunological response to these lesions. One of our patients presented with metastatic disease, and another developed metastasis during treatment, similar to an earlier series of mucosal melanoma in which metastasis predated the diagnosis of primary in almost 33% of the cases[51].

Given the small number of the cases of vaginal melanoma reported in the literature, and the large time span over which they have been reported, limited data is currently available to base recommendation for the primary management of patients with MMV. Similarly, infrequent incidence of this disease makes it difficult to do any meaningful prospective studies. Hence, what should be the best treatment for vaginal melanomas remains controversial. There is no significant difference in survival observed with the use of different treatment regimens whether alone or in combination[11,52,53].

Local excision has been shown to invariably result in local recurrence and subsequent widespread metastasis[6,54]. Bonner et al[14] pooled data from 6 series, where patients received conservative treatment and found that all the 10 patients developed recurrent disease in loco-regional sites at some point of time. However, encouraging results with 5-year survival rate of 64% were shown by Konstadoulakis et al[55] they attributed this to early stage of presentation and 2-cm margin achieved in almost all cases.

Many authors have stressed the importance of radical surgical resection supplemented by dissection of regional lymphatics, for even the most minimally invasive melanomas of the vagina in order to reduce the risk for local recurrence[12,16,56,57]. It is difficult to ascertain which patient would make good candidates for radical therapy. There appears to be a selection bias, with younger patients and smaller lesions being offered more radical sugery than older patients and larger lesion probably with the hope of better outcome. Van Nostrand et al[12] in their 8 cases showed a survival benefit in a radical group with 50%; 2-year survival compared to 20% survival in the conservative group for lesion less than 10 cm^2. However, there was no improvement in survival at 5-years. Bonner et al[14] in their pooled analysis showed that even radical surgical procedure results in a high rate of loco-regional failures (13/18). In the present report too one patient in radical group failed locally at 13 months. Is such radical resection is truly necessary? There is no convincing evidence that extended surgical procedures are appropriate, given the high rate of metastasis frequently found at initial diagnosis. It might be possible to achieve similar, if not improved loco-regional control without the attendant surgical and psychological morbidity associated with such radical and often disfiguring procedures by other means[53].

Radiation therapy has earlier been regarded as ineffective for malignant melanoma at any site as in the in vitro survival curve of cutaneous melanomas shows a wide shoulder, indicating a great ability of these cells to repair sublethal damage[58]. Several authors have reported isolated cases of good local control when radiation was employed for vaginal melanomas[16,59,60] but long-term analysis has been limited by the death from disseminated disease.

Moreover, as indicated earlier, cutaneous melanomas higher rates of partial and complete regression are noted with the use of high dose individual fraction (≥400 cGy per fraction) compared to conventional dose treatment of 180 cGy per fraction[14,61]. Harwood et al[62] treated mucosal melanomas of the head and neck region with high irradiation fraction and obtained an 85% complete remission rate, compared with only 28% complete remission rate with smaller fractions. High fractionation using 6–8 doses of external beam radiation of 6 Gy, 1 week apart, to the vaginal primary and the inguinal nodes is tolerated as well and has shown to provide a high local control rate and even few long-term surviors[62–64]. William et al[23] treated two cases with wide local excision followed by subsequent high dose fraction vaginal irradiation and found that regional control was better without the attendant surgical and psychosocial morbidity seen with radical surgical extirpation, Bonner et al[14] suggested that preoperative morbidity seen with radical surgical extirpation. Bonner et al[14] suggested that preoperative radiotherapy given in high individual treatment doses (500 cGy X 6; given 3 days a week to the whole pelvis) with subsequent consideration for a vaginal boost field followed by total vaginectomy and resection of gross residual disease may improve the poor rates of local control and survival that are seen with either of the treatment used alone. The complications of high fractionation for pelvic radiotherapy can be avoided by decreasing pelvic field[63].

Despite improvements in survival of extra genital cutaneous melanomas with systemic therapy (chemotherapy and interferon), no such improvement has been seen in patients with vaginal melanomas. Combination chemotherapy with fotemustine, DTIC and concurrent systemic therapy with interferon α-2-b has been shown to produce partial remission of one year after surgical treatment[64]. Treatment with human leukocytes and a interferon results in an increase in T4 cell count and enhancement in the ratio

of CD4 to CD8 cells suggesting its major role in boosting immune system[65]. Adjuvant interferon-α also confers survival benefit in patients with nodal disease[17]. Combination chemotherapy comprising carmustine, DTIC, cisplatin and tamoxifen showed response rate of 60% with a median survival of 11.5 months and no complete response. This regimen is a fairly active combination against metastatic melanoma, particularly those with metastases to the nodes, skin, and the lung[66].

Despite the rarity of MMV, this entity should always be kept in mind when discussing the clinical approach to aged women. Curative treatment should begin only when metastatic workup is negative (isotope bone scan and CT scan chest). Because of the problems of poor loco-regional control and poor overall survival seen with current treatment regimens, the role of novel therapeutic strategies like high dose fraction irradiation (>400 cGy / fraction) needs to be defined. Such primary therapy with high dose fraction radiation would preclude the need for radical surgical extirpation, which despite its attendant morbidity, has failed to consistently demonstrate improvements either in loco-regional control or in overall survival. The role of elective lymph node dissection and radical resection remains controversial.

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