Section: Surgical Oncology

Case Series

# MUCOSAL MELANOMA: EPIDEMIOLOGY, CLINICAL FEATURES, AND SURGICAL MANAGEMENT

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ABSTRACT

**Background: Purpose of Review:** Summarize the cases of mucosal melanoma that attended The Department of Surgical Oncology of SSKM Hospital.

**Recent Findings:** New research has demonstrated a difference between Mucosal Melanoma and cutaneous melanoma in their genomic and molecular landscapes, explaining the response's heterogeneity. Immunotherapy and targeted therapy have limited benefit, but novel therapies are rapidly expanding.

**Summary:** Mucosal melanoma is aggressive cancer occurring in gastrointestinal, respiratory, or urogenital mucosa; whose incidence is greater in the Asian population. The etio-pathogenesis remain unclear since UV exposure is not a proven risk factor as in cutaneous melanoma.

**Keywords:** Mucosal Melanoma, Cancer.

## INTRODUCTION

Melanoma is a cancer of melanocyte and can therefore arise in skin, mucosa, retina and leptomeninges. Melanoma arises from malignant transformation of melanocytes, the cell responsible for production of pigment melanin. Precursor melanocytes arise in the neural crest and as the fetus develops, migrate to multiple areas in the body including the skin, meninges, mucous membranes and eyes. To date, the risk factors are poorly understood and the pathogenesis remains unclear,[1] although an association with human papillomavirus and herpesvirus has been described.[2] In contrast to Cutaneous Melanoma, the diagnosis of mucosal evolutive lesions is more difficult and Mucosal Melanoma is therefore likely to be detected at a late stage.[3] The overall five-year survival rate for Mucosal Melanoma is 10–20%.[2] Here, we present a comprehensive review of different primary Mucosal Melanoma, their epidemiological and clinical features, and surgical management of the patients who attended Department of Surgical Oncology of IPGMER and SSKM Hospital, Kolkata.

## GENOMICS

Mutation Landscape- Genetically, Cutaneous Melanoma can be categorized as BRAF-mutant (50%), RAS-mutant (20%-30%), NF1-mutant (10%-15%), or triple wild-type (10%-15%).[4] However, Mucosal melanoma is driven by distinct mechanisms from Cutaneous melanoma with SF3B1-mutant (15%), NF1- mutant (14%), KIT-mutant (13%), NRAS-mutant (8%), and BRAF (6%).[5] Subtype specific, Sun et al,[6] identified MUT16 (11/44, 25%) and KMD2T (8/44, 18.18%) were recurrently mutated in anorectal and gynecologic melanoma. Cui et al,[7] identified PDGFRA was most common in head and neck melanoma (23/96, 23.96%). Brandon reported that ROS1 also has a high frequency in head and neck melanomas, ranked third after NRAS and NF1 mutations. They also identified that no driver mutations provided overall survival (OS) benefits, except ROS1, which seems likely because of higher tumor burden (TMB).[8]

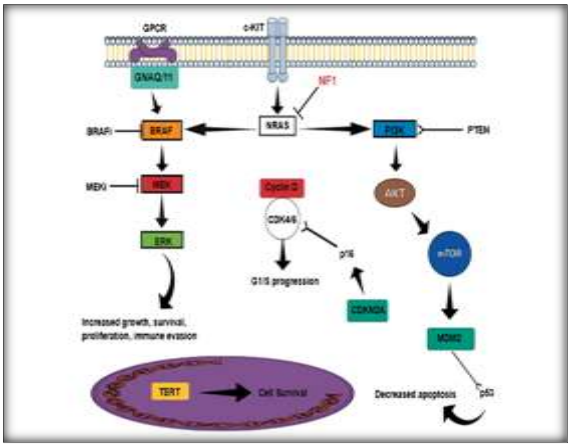


**Figure 1: Signalling pathways in Melanoma**

## EPIDEMIOLOGY

Mucosal melanoma is a rare and aggressive subtype. The incidence of Mucosal melanoma is influenced by age, with more than 65% of patients over 60 years of age and less than 3% under 30 years of age. Racial differences in incidence have been reported. Asians have a higher incidence of Mucosal melanoma arising from the anorectal tract, whereas non-Hispanic whites have a higher incidence of genitourinary Mucosal melanoma.[9]

## ETIOPATHOGENESIS

Based on recent studies, melanocytes produce many molecules in consequence of UV exposure as cytokines, melanocortin, amines, and nitric oxide (NO), thus promoting melanogenesis. Notably, Mucosal Melanoma is not associated with UV exposure.[10] Because the pathogenesis of Mucosal Melanoma is unrelated to typical carcinogens, there is poor evidence to support a link between cigarettes, formaldehyde, or exposure to cancer-causing viruses (i.e., papillomavirus, herpes virus, or polyomavirus).[11] For example, melanocytes could play a key role in the metabolization of polycyclic aromatic hydrocarbons.[12,13]

### Mucosal Melanomas of the Gastrointestinal Tract:

Mucosal melanoma frequently affects the oral cavity and the anal canal (33% and 31% of patients respectively), while other sites such as the oesophagus, stomach, small intestine, or gallbladder are rarely involved. Only 14% of patients with primary Mucosal Melanoma of the gastrointestinal tract are under the age of 50, and about 50% are over the age of 70.[14] On endoscopy, lesions appear hyperpigmented and ulcerated with satellite nodules.[15]

Anal and rectal melanoma occurs most commonly in the seventh decade of life, with a higher incidence in women and a prevalence in Caucasians.[16] It causes rectal bleeding, pain or discomfort and is often diagnosed at an advanced or metastatic stage.

### Mucosal Melanomas of the Urogenital Tract:

Urogenital tract melanoma is more common in females of Caucasian ethnicity in about 90% of cases.[17] The female genital tract accounts for 18% of Mucosal Melanoma and 3% of those of the urinary tract; the most common site is vulvar (76.7%) followed by vaginal (19.8%), while cervical melanoma is the least common. Symptoms include bleeding, lumps or masses in the vulvar area, itching, pain or irritation, discomfort, and discharge.[18] Pain, mass lesions, and vaginal bleeding and discharge are the most typical presenting symptoms.[19] It appears macroscopically as a variety of pigmented lesion that is fragile, easily bleeds, and ulcerated in half of the cases. Melanoma of the cervix is extremely rare,[20] and appears as a variously pigmented or amelanotic exophytic cervical mass. Melanoma of the urethra accounts for about 4% of all urethral malignancies.[21]

In about 20% of cases, Mucosal Melanoma of the urethra is amelanotic and has polypoid growth, therefore is mistaken for a urethral polyp, mucous prolapse, or urothelial tumor.[22]

## DIAGNOSIS

When diagnosing primary mucosal melanoma, especially in some sites on which it rarely arises, it is of crucial importance to exclude possibility of metastatic lesion from primary cutaneous or ocular melanoma. Presence of in situ melanoma or radial growth phase is important for distinguishing primary lesions from metastases.[23] Allen and Spitz,[24] defined as main criteria for diagnosis of primary melanoma junctional or in situ melanoma component with intact epithelium overlaying invasive melanoma. However, because of hidden location and lack of early symptoms, diagnosis of mucosal melanomas is usually delayed and many lesions are ulcerated at diagnosis, so this criterion is not easy to assess. Amelanotic appearance which is not rare among mucosal lesions, makes diagnosis even more difficult. Immunohistochemical staining positive for protein S-100, HMB-45, Melan-A, Mart-1 and tyrosinase support diagnosis of melanoma.

## STAGING:

There is no universal staging system for mucosal melanomas. Various staging systems are in use for various locations. However, in the seventh edition of The American Committee on Cancer (AJCC) cancer staging manual, it was given tumor–node–metastasis (TNM) staging system for mucosal melanoma of the head and neck.[25]

## TREATMENT GUIDELINES:

There are no randomized trials studying treatment modalities such as surgery, radiotherapy, or chemo-/immunotherapy specifically in mucosal melanoma. Surgical resection remains the treatment of choice and can result in cure.[26] Interferon-alpha-2b is frequently offered to mucosal melanoma patients as systemic adjuvant therapy.

Novel agents for the treatment of advanced melanoma are being extensively investigated and patients with mucosal melanoma are eligible for most clinical trials in melanoma. A study by Curtin et al,[27] in 2006 shed light on c-KIT genetic alterations in melanoma. That study showed that c-

KIT amplification/mutation occurred in 39% of mucosal melanomas, but none of non– chronic sun damage cutaneous melanoma cases. Mucosal melanoma has been shown to exhibit amplifications or increased copy numbers of the 4q12 locus by comparative genomic hybridization. Mutations, including the activating K462E mutations of the c-KIT kinase domain, which are known to render sensitivity to imatinib (a tyrosine kinase inhibitor) in gastrointestinal stromal tumors, are also commonly seen in mucosal melanoma. The prevalence of these mutations in mucosal melanoma is 5%–22% based on some studies,[27,28,29] which is much lower than what was originally expected. Preclinical studies have shown sensitivity of c-KIT mutant mucosal melanoma, providing a rationale for studying imatinib in this melanoma type in clinical trials. Marked tumor regression was reported in a patient with metastatic mucosal melanoma who was treated with single-agent imatinib.[30] This observation has been substantiated by several other anecdotal reports, demonstrating objective responses in patients with advanced mucosal and acral melanoma after imatinib monotherapy.[31,32]

**PROGNOSIS AND OUTCOME**

Primary melanoma arising in the mucous membranes is an aggressive disease. The best likelihood for favourable outcome is early detection and excision. Local recurrence is usually a harbinger for concurrent or subsequent distant metastases.[33,34] Distant spread in general is associated with rapid clinical deterioration and a short survival time.[35,36]

**ANO-RECTAL MELANOMA:**

**CASE-1:**

A 57-year-old woman presented to Department of surgical Oncology OPD, SSKM, referred from Department of Radiotherapy, with h/o per rectal bleeding for last 2 months. Per-Rectal examination revealed a 5*5 cm mobile growth at 5 to 8 O' clock position in the anal canal, approximately 2cm from the anal verge. Colonoscopy identified an Irregular mass in the Ano-Rectal region, starting 2cm from anal verge. Upper extent could not be felt. A Colonoscopy guided biopsy of which showed Malignant Melanoma. An 18F FDG Whole Body PET–CT scan demonstrated FDG avid heterogeneously enhancing intra luminal soft tissue mass lesion in the lower rectum, measuring approximately 4.7 x 4.3 cm with SUV max 8.7. The lesion is 4.3 cm from anal verge. No obvious Meso-rectal infiltration noted-Primary neoplastic site. No other significant locoregional or distal metastasis in rest of the whole body. The patient underwent a Laparoscopic Abdomino-pelvic resection operation. Post operative histopathology report showed a blackish polypoid tumor of 6 cm in its greatest axis, 27 cm from proximal and 2 cm away from distal margin. On microscopic examination, tumor showed malignant melanoma. Patient was on regular follow up. Approximately 6 months after the APR, patient developed a recurrent disease in the posterior-most aspect of perineal surgical scar site. The follow up PET CT scan revealed a localized recurrence [FNAC of the lesion confirmed the recurrence]. The patient underwent wide local excision of the recurrent Melanoma. Post-operative HPE revealed blackish nodule of 5.1 cm x 4 cm x 4 cm. Microscopic examination showed nodular tumor situated in Dermis and sub-cutaneous tissue composed of nests and sheets of oval to polygonal cells having pleomorphic nuclei having distinct nucleoli and eosinophilic cytoplasm. Mitotic figures seen. Cytoplasm contains Melanin-s/o Malignant Melanoma. All surgical resection margins were free. The patient is on regular follow-up.

**CASE-2:**

A 54-year-old woman presented to Department of surgical Oncology OPD, SSKM with h/o per rectal bleeding for last 2 months. Per-Rectal examination revealed a 6 x 7 cm mobile growth at 6 to 9 O' clock position in the anal canal, approximately 2cm from the anal verge. Colonoscopy identified a polypoidal ulcerative mass just beyond the anal verge. A Punch biopsy from the growth showed Mucosal Melanoma. A 18F FDG Whole Body, CECT Whole Abdomen + Chest scan demonstrated no metastatic lesions. Meso-rectal infiltration noted in MRI PELVIS. No other significant locoregional or distal metastasis in rest of the whole body. The patient underwent a Laparoscopic Abdomino-pelvic resection with total meso-rectal excision. Post operative histopathology report showed a pigmented ulcero-nodular tumor of 9cm x 6cm x 5cm which was 1.5 cm away from distal margin and 25 cm from proximal resection margin. On microscopic examination, tumor showed malignant melanoma [pT3aN0]. IHC study was done which showed HMB-45 and MELAN-A positive and PDL-1 negative. Patient is on regular follow up.

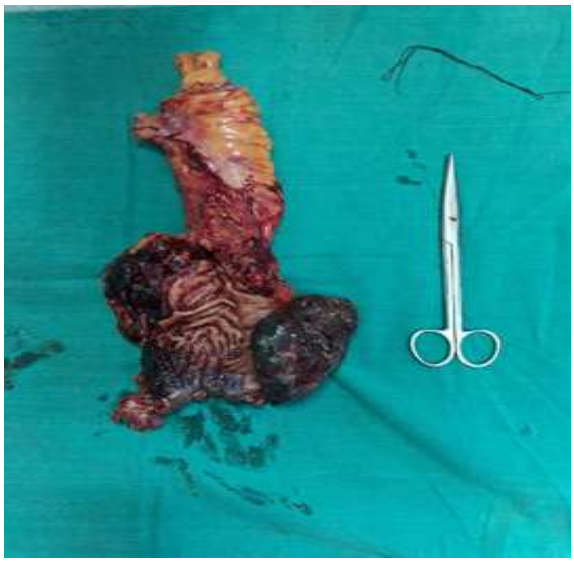

**Figure 2: Specimen of Abdomino-Pelvic Resection operation, cut open along its length showing the lesion**

**CASE-3:**

A 55-year-old woman presented to Department of surgical Oncology OPD, SSKM with h/o altered

bowel habits for last 3 months. Colonoscopy identified an ulcero-proliferative rectal growth involving the Ano-Rectal junction extending for 5cm. The Colonoscopy guided biopsy was suggestive of poorly differentiated Malignant Neoplasm. HPE of anal punch biopsy revealed Malignant Melanoma; IHC- MELAN-A, HMB-45 and S-100 positive, PAN-CK negative. An 18F FDG Whole Body PET–CT scan demonstrated soft tissue mass lesion of 6 x 5.2 x 5.8 cm involving the rectum, Ano-Rectal Junction and Anal canal [SUV max 7.0]. No other significant locoregional or distal metastasis in rest of the whole body. The patient underwent an Abdomino-pelvic resection with total meso-rectal excision. Post operative histopathology report showed an irregular lesion of 5 cm in its greatest axis, 21 cm from proximal and 4 cm away from distal margin. On microscopic examination, tumor showed malignant melanoma. Patient is on regular follow up.

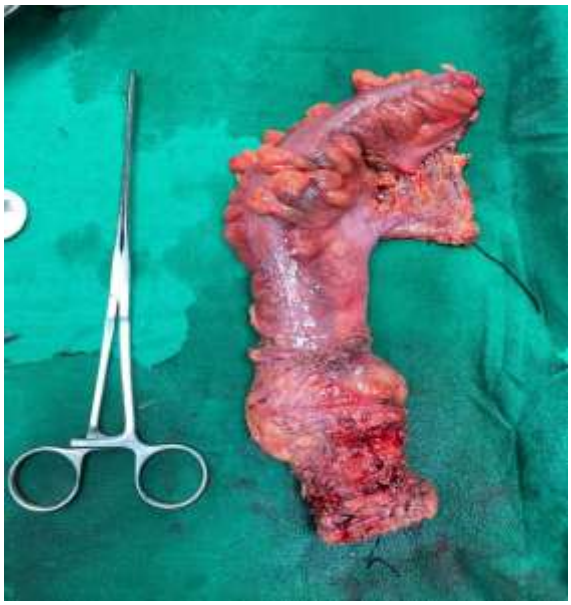

**Figure 3: Specimen of APR done for Ano-rectal Melanoma**

Anorectal melanoma is rare and accounts for 0.4%–1.6% of all melanoma cases.[37] In one large series, anorectal melanomas represented 0.5% of all colorectal and anal cancers.[38] Similar to melanomas of the female genital tract because of the contiguity of the mucosal and cutaneous tissues, it is important to define the exact anatomic location of anal melanomas because many of them may actually be cutaneous in origin. Like anorectal carcinomas, the diagnosis of anorectal melanoma is often delayed because typical symptoms such as anal pruritus or rectal pain can mimic benign conditions, such as hemorrhoids or rectal polyps. The majority of anal melanoma lesions arise near the dentate line in the anal canal. Although risk factors are largely unknown, an association with HIV infection has been suggested.[39] Prognostic factors include stage at diagnosis, lymph node status, and tumor thickness. Prognosis in general for anorectal melanoma is poor, with a 5-year survival rate of about 20% from several studies.

**MALIGNANT MELANOMA OF THE FEMALE GENITAL TRACT:**

**CASE-4**

A 55-year-old woman with a past history of sub-urethral pigmented growth for which she underwent excisional biopsy in a private hospital, presented to Department of surgical Oncology OPD, SSKM, complaining of recurrence of growth in same location. Previous excisional biopsy was reported as poorly differentiated malignancy favouring melanoma, thickness >4mm, mitosis: 20/10 hpf. IHC study showed S 100, HMB 45 and SOX 10 positive. She also gave history of Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy surgery done 3 months prior for refractory dysmenorrhoea and HPE report revealed chronic cervicitis and fibroid uterus. Physical examination revealed sub-urethral black pigmented growth involving anterior and posterior vaginal walls. MRI Pelvis showed ill-defined T1/T2 hyperintensity along urethral meatus and vulva, involving anterior and lower posterior vaginal wall. CECT Whole abdomen + chest showed no metastatic lesion. Surprisingly 18F FDG whole body PET-CT scan showed no evidence of metabolically active residual or recurrent disease. Patient was taken up for surgery after pre-operative workup and Urology consultation. En-block excision of vulva, complete urethra, vagina and bilateral pelvic lymph node dissection and bilateral inguinal lymph node dissection followed by closure of bladder apex followed by permanent supra-pubic cystostomy was done for this patient. Post operative HPE was reported as 1.5x1.5 cm Mucosal Melanoma [pT4aN0], depth of invasion- 6mm, margins free, B/L pelvic lymph nodes: 0/8 and B/L inguinal lymph nodes: 0/32. Patient was on regular follow-up. However, 9 months after surgery she developed a pelvic wall recurrence that was deemed unresectable.

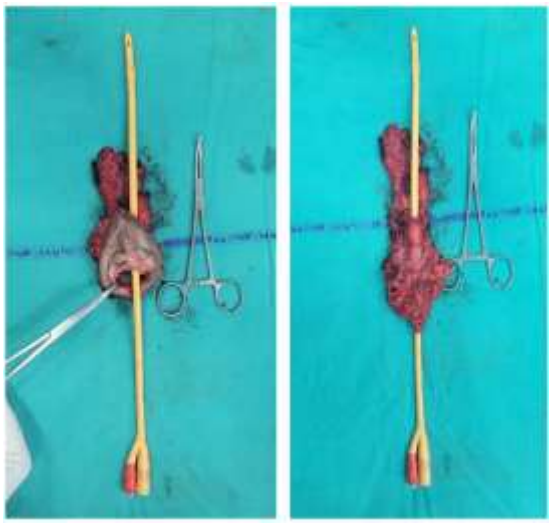

**Figure 4: Showing anterior and posterior aspects of specimen with Foley catheter in-situ**

**Figure 5: showing Melanoma in sub urethral region and vagina.**

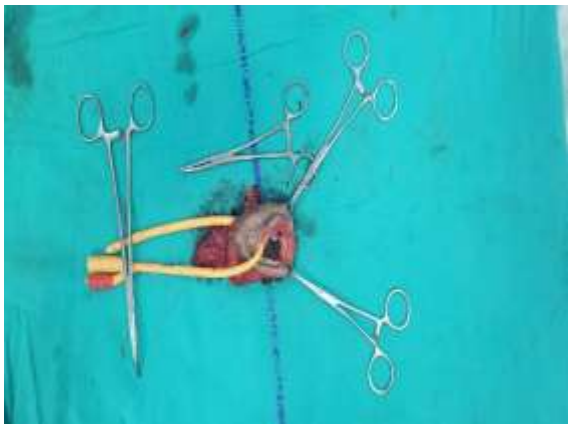

**Figure 6: Vaginal vault everted and foley catheter in-situ in urethra**

Although rare, melanoma can arise in almost any part of the urogenital tract, including vulva and vagina, uterine cervix, urethra and urinary bladder. Mucosal melanomas of the urogenital tract are more common among women. Female genital tract accounts for 18% of all mucosal melanomas, and urinary tract melanomas for about 3%.[40] Among female genital tract, the most common is vulvar melanoma (76.7%) followed by vaginal (19.8%), while cervical melanoma is least common.[41]

Melanoma of the vagina is very rare, with less than 300 cases reported in literature, and accounts for less than 3% of all vaginal malignancies.[20] Vaginal melanoma is mainly a disease of elderly women, and predominantly occurs in white individuals. It most commonly affects postmenopausal women (80%), and mean age at diagnosis is around 60 years.[42,43] The most common presenting symptoms are vaginal bleeding and discharge, presence of mass lesion, and less common pain.[42] In about 20% of cases, disease is multifocal.[43] Size of tumor appears to be the most predictive for survival, and tumors <3cm in size have better survival.[42] Surgery is the best available treatment for vaginal melanoma. Prognosis of vaginal melanoma is poor regardless therapy, and reported five-year survival rates are ranging from 0 to 21%.[42]

Melanoma of the urethra is very rare tumor and account for about 4% of all urethral malignancies.[22] Distal urethra is the most common site of occurrence of melanoma in urinary tract. It mostly occurs in elderly patients, and more common in females. Surgery is the main treatment option, but optimal extent of surgery remains undefined.[22]

## CONCLUSION

Primary mucosal melanomas are very rare but aggressive tumors. Compared with cutaneous (80.8%) and ocular melanomas (74.6%), mucosal melanomas have the lowest percent of five-year survivals, only 25%. For now, best hope for survival offers early detection and complete surgical removal. However, because of occult site of occurrence and unspecific symptoms, diagnosis is usually delayed. Each anatomical site requires specific surgical approach, and in many cases complete removal of tumor is limited by surrounding structures. Recently revealed genetic changes underlying mucosal melanomas offer new hope for development of more effective systemic therapy for these aggressive tumors. Since risk factors are not well known, improvement of prevention seems not possible. Any pigmented lesion on mucosal membranes and mucocutaneous junctions deserves attention. It is very important that clinicians have on mind these rare sites of occurrence of melanoma, especially because some of them are accessible for examination, such as oral or genital tract, and could be detected at an earlier stage.

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