Dermatology Practical & Conceptual

Clinical Review of Mucosal Melanoma: The 11-Year Experience of a Referral Center

Marco Spadafora[1,2], Giacomo Santandrea[1,3], Michela Lai[1,2], Stafania Borsari[2], Shaniko Kaleci[4], Chiara Banzi[5], Vincenzo Dario Mandato[6], Giovanni Pellacani[7], Simonetta Piana[3], Caterina Longo[2,4]

1 Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy
2 Centro Oncologico ad Alta Tecnologia Diagnostica, Azienda Unità Sanitaria Locale - IRCCS di Reggio Emilia, Reggio Emilia, Italy
3 Pathology Unit, Azienda Unità Sanitaria Locale - IRCCS di Reggio Emilia, Reggio Emilia, Italy
4 Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy
5 Medical Oncology Unit, Azienda Unità Sanitaria Locale - IRCCS di Reggio Emilia, Reggio Emilia, Italy
6 Unit of Obstetrics and Gynecology, Azienda Unità Sanitaria Locale - IRCCS, Reggio Emilia, Italy
7 Dermatology Clinic, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

Key words: mucosal melanoma, diagnosis, treatments, rare disease

Citation: Spadafora M, Santandrea G, Lai M, et al. Clinical Review Of Mucosal Melanoma: The 11-Year Experience Of A Referral Center. *Dermatol Pract Concept.* 2023;13(1):e2023057. DOI: https://doi.org/10.5826/dpc.1301a57

Accepted: June 29, 2022; **Published:** January 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Caterina Longo, Department of Dermatology, University of Modena and Reggio Emilia, Italy. Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Centro Oncologico ad Alta Tecnologia Diagnostica-Dermatologia, Reggio Emilia, Italy. Phone: +390522295612 E-mail: longo.caterina@gmail.com

ABSTRACT

Introduction: Mucosal melanoma is a rare neoplasm. Late diagnosis is caused by occult anatomic sites and scarcity of symptoms. Novel biological therapies have now become available. Demographic, therapeutical and survival records on mucosal melanoma are scarce.

Objectives: To provide an 11-year retrospective clinical review of real-world data on mucosal melanomas managed in a tertiary referral center in Italy.

Methods: We included patients with histopathological mucosal melanoma diagnoses from January 2011 to December 2021. Data were collected until the last known follow-up or death. Survival analysis was performed.

Results: Among 33 patients, we found 9 sinonasal, 13 anorectal and 11 urogenital mucosal melanomas (median age 82, females 66.7%). Eighteen cases (54.5%) presented with metastasis ($p<0.05$).

In the urogenital subgroup, only 4 patients (36.4%) had metastasis at diagnosis, all in regional lymph nodes. Sinonasal melanomas were surgically managed with a debulking procedure (44.4%); every case of anorectal and urogenital melanomas underwent radical surgery (30.8% and 45.5%). Fifteen patients were treated with biological therapy ($p<0.05$). Radiation therapy was used in all melanomas of the sinonasal region ($p<0.05$). Overall survival was longer for urogenital melanomas (26 months). Univariate analysis showed an increased hazard ratio for death in patients with metastasis. A negative prognostic value of metastatic status was reported by the multivariate model, while administration of first-line immunotherapy demonstrated a protective role.

Conclusions: At diagnosis, the absence of metastatic disease is the most relevant factor that influences the survival of mucosal melanomas. Moreover, the use of immunotherapy might prolong the survival of metastatic mucosal melanoma patients.

Introduction

Melanoma is a malignant tumor arising from melanocytes [1]. Although melanocytes are mostly localized in the skin, their precursors reach also endodermal and ectodermal mucosae migrating from the neural crest [2]. Primary mucosal melanoma arises from mucosal membranes lining the head and neck (i.e. nasal and oral cavities), anorectal, vulvovaginal, and urinary tract in order of frequency [3,4]. The occult locations in which mucosal melanoma occurs preclude sun exposure as a predisposing risk factor; the etiologic factors driving tumorigenesis in mucosal melanoma have not been discovered yet [5]. Mucosal melanoma represents 0.03% of all cancer diagnoses and 0.8-3.7% of all melanomas [5,6], with a higher incidence in women than men; different gender incidence is mainly due to vulvovaginal neoplasia, which represents alone 18% of mucosal melanomas [1].

Most patients with mucosal melanoma are diagnosed in a metastatic stage because of the late occurrence of symptoms and the occult location of the primary tumor [7]. The most common symptoms in nasal cavity melanomas are unilateral nasal obstruction, mass lesion, and epistaxis while in the oral cavity symptoms such as swelling, ulceration, bleeding, pain, or tooth mobility can occur. Anorectal melanomas usually manifest with rectal bleeding, anorectal discomfort, or prolapse of the tumor mass. In vulvovaginal melanomas presenting symptoms are bleeding, vulvar mass, pruritus, pain or irritation, micturition discomfort, and discharge [4].

There is no universal staging system for mucosal melanomas. Head and neck mucosal melanomas are usually staged according to the American Joint Committee on Cancer (AJCC) criteria for head and neck cancer; vulvar melanoma can be staged following the AJCC criteria for cutaneous melanoma, while no staging criteria have been established for mucosal melanoma arising in the urethra, vagina, rectum, and anus [8].

Surgical excision with negative margins, which is the treatment of choice in mucosal melanomas, is often unfeasible because of an anatomically complex site of origin [7,9]. Patients with unresectable or metastatic mucosal melanomas can be treated with the same regimen proposed for cutaneous melanoma [10], although the frequency of common driver BRAF is low compared to the cutaneous counterpart (50% vs 3-5%), with reduced usefulness of targeted therapy [1]. Mutation of the *KIT* gene is detected in about 25% of mucosal melanomas [1]; to date, guidelines suggest KIT testing only when BRAF and, eventually, NRAS, mutational status have been established; KIT targeted therapy is usually administered as a second line therapy [8]. In the last few years, immune checkpoint inhibitors (ICIs) have become a preferred first-line approach for patients with advanced or metastatic cutaneous melanoma. A recent review [7] showed that anti-CTLA-4 antibody ipilimumab has less efficacy as monotherapy than monoclonal antibodies targeting the PD-1 and PD-L1, which have proven more effective in the treatment of MMs, with prolonged survival and acceptable toxicity. A sub-analysis of mucosal melanomas performed in a five-year survival trial showed similar data on efficacy [8,11]. The treatment regimen currently authorized by *Agenzia Italiana del Farmaco* for advanced mucosal melanoma includes ipilimumab and anti-PD1 antibodies, while Imatinib is approved for unresectable metastatic melanoma in progression after immunotherapy [8].

As primary mucosal melanoma is an exceedingly rare neoplasm, demographic, histopathological, therapeutical, and survival records on this topic are scarce. The current study aims to provide an 11-year retrospective clinical review of the real-world data on mucosal melanomas managed in a tertiary referral center in Italy.

Methods

This was a retrospective study performed between 01/01/2011 to 31/12/2021. This study was approved by the Institutional Review Board of Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Italy (protocol number #2011/02347213).

We included consecutive patients with a histopathologically confirmed diagnosis of mucosal melanomas. We excluded recurrent tumors, unknown primary melanomas, and cases for which histological slides were not available for re-evaluation.

Data from the first clinical or instrumental diagnosis to the date of each patient's last known follow-up appointment or death was obtained from digital medical records. We recorded patient age, gender, location of the lesion, presenting symptoms, site of metastasis at diagnosis if any (locoregional lymph node involvement, cerebral, visceral, or multiple metastases when more than one of the previous sites was involved) and histopathological and molecular features (cell morphology, Breslow thickness and ulceration when not compromised by fragmentation or orientation of biopsy specimen, and mutational status).

Surgery was recorded as debulking procedure or radical treatment. Systemic treatments were categorized according to current recommendations [8,10] as first-line biological treatment (nivolumab, pembrolizumab, or imatinib), as first-line chemotherapy when the patient was administered with systemic therapy in the pre-biological era, and as second-line treatments when therapy was switched to a different therapy because of disease progression. We also recorded if the patient underwent radiation therapy on the primary tumor, which was always managed with a cytoreductive-palliative purpose in our series [12].

Statistics

Statistical analysis was performed using STATA® software version 17 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). Descriptive statistics were presented for baseline demographic clinical characteristics for the entire group, as well as for the groups of patients with different locations. Continuous variables were presented as the number of patients (N), mean, standard deviation (SD), minimum (min), and maximum (max) and compared between subgroups using Unpaired Student's t-test; categorical variables were presented as frequency (N, percentage [%]) and compared using Pearson's chi-squared test. Survival analysis was performed using the Kaplan-Meier method and comparison between the survival curves was done using log-rank test. Univariate and multivariate analyses were done using the Cox-regression hazard model. Data from the univariate and multivariate regression analyses were expressed as Hazard ratio (HR) with it 95% confidence interval (CI). A $p<0.05$ was considered statistically significant.

Results

Demographic, Clinical, and Treatment Data

Among 33 patients with primary mucosal melanomas who were included in our analyses, we found 9 melanomas of the sinonasal region, 13 anorectal melanomas and 11 urogenital melanomas (of which 10 vulvovaginal melanomas and 1 bladder melanoma), as reported in Table 1 and Figure 1. Median age at diagnosis was 82 years (75-83), with no substantial differences by anatomical site. More women than men had mucosal melanoma (n= 22, 66.7%). Median follow-up period was 11.5 months.

Presenting symptoms for which physicians were consulted by the patient were recorded in Table 2 (in our series dermatologists, otolaryngologists, gynecologists, and endoscopists); most patients were then managed by the Skin Cancer Tumor Board.

We observed that 18 cases of mucosal melanoma (54.5%) out of 33 presented with metastasis at diagnosis ($p<0.05$) and that 91% and 66% of patients with anorectal and sinonasal melanomas had at least one metastatic site at diagnosis. In urogenital melanomas, 4 out of 11 (36.4%) showed metastases which were all diagnosed in locoregional lymph nodes (inguinofemoral nodes) and no distant metastases.

Surgery: Clinical records reported that 39.4% of patients underwent surgical treatment ($p<0.05$). All the sinonasal melanomas which were surgically managed (44.4%) underwent a debulking procedure, while every surgically managed anorectal and urogenital melanoma had a radical intent procedure (30.8% and 45.5%). Most patients did not undergo surgery because of metastasis at diagnosis (n=14), detection of different neoplasia at primary staging (n=2), unresectable tumor (n=3), age of the patient (n=1), death of the patient before surgery (n=1).

Systemic treatment: We identified 15 patients treated with systemic biological therapy as first-line treatment ($p<0.05$); 13 received nivolumab, 2 subjects were treated with pembrolizumab and 1 subject with imatinib. Only 1 patient received first-line chemotherapy (cyclophosphamide, vincristine, and dacarbazine combination treatment).

Furthermore, 5 patients were switched to a second-line systemic therapy; 3 of them were switched to ipilimumab, 1 to pembrolizumab and 1 to monotherapy with dacarbazine.

Radiation therapy (RT): in our analysis, RT on the primary tumor has always been proposed as a cytoreductive-palliative treatment; it was performed in all cases of sinonasal melanoma ($p<0.05$). Anorectal melanomas were treated with RT

Table 1. Comparison of demographic, clinical, and survival data in patients with mucosal melanomas and stratification by the site of origin.

	Mucosal melanomas (n=33, 100%)	Sinunasal (n=9, 27.3)	Anorectal (n=13, 39.4%)	Urogenital (n=11, 33.3%)	p-value
Age at diagnosis, median (IQR)	82 (75-85)	82 (75-83)	80 (72-87)	83 (80-85)	0.977
Female	22 (66.7)	5 (55,6)	6 (46,2)	11 (100)	**0.015**
Metastasis at diagnosis	18 (54.5)	4 (44,4)	10 (76.9)	4 (36.4)	
Regional lymph nodes	8 (24.2)	0 (0.0)	4 (30.8)	4 (36.4)	
Visceral	4 (12.1)	3 (33.3)	1 (7.7)	0 (0.0)	**0.021**
Cerebral	2 (6.1)	0 (0.0)	2 (15.4)	0 (0.0)	
≥2 sites	4 (12.1)	1 (11,1)	3 (23.1)	0 (0.0)	
Surgical treatment	13 (39.4)	4 (44.4)	4 (30.8)	5 (45.5)	
Debulking	4 (12.1)	4 (44.4)	0 (0.0)	0 (0.0)	**0.015**
Radical excision	9 (27.3)	0 (0.0)	4 (30.8)	5 (45.5)	
First-line biological therapy	17 (51.5)	5 (55.5)	6 (46.2)	5 (45.5)	
Nivolumab	13 (39.4)	4 (44.4)	4 (30.8)	5 (45.5)	**0.005**
Pembrolizumab	2 (6.1)	1 (11.1)	1 (7.7)	0 (0.0)	
Imatinib	1 (3.0)	0 (0.0)	1 (7.7)	0 (0.0)	
First-line chemotherapy	1 (3.0)	1 (11.1)	0 (0.0)	0 (0.0)	0.253
Second-line systemic therapy	5 (15.1)	2 (22.2)	2 (15.4)	1 (9.1)	
Ipilimumab	3 (9.1)	2 (22.2)	1 (7.7)	0 (0.0)	0.383
Pembrolizumab	1 (3.0)	0 (0.0)	1 (7.7)	0 (0.0)	
Dacarbazine	1 (3.0)	0 (0.0)	0 (0.0)	1 (9.1)	
Radiation therapy on the primary tumor	17 (51.5)	9 (100)	6 (46.2)	2 (18.2)	**0.004**
Overall survival, median (IQR) months	11 (6-25)	14 (6-22)	6 (2-11)	26 (11-34)	0.021
Overall survival rate%, 12 months	71	55	54	100	
Overall survival rate%, 12 months	54	37	18	100	
Median follow-up period (months)	11.5	-	-	-	

IQR: interquartile range

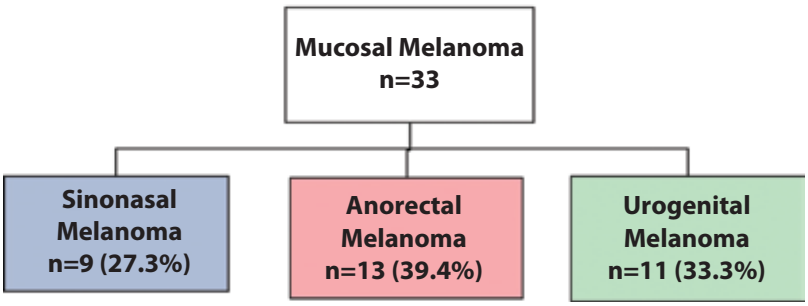

Figure 1. Flow diagram showing mucosal melanoma subdivided by anatomical site of origin.

Table 2. Presenting symptoms of mucosal melanoma by anatomical region.

	Presenting symptoms (n)
Site of primary melanoma	
Sinonasal	Epistaxis (2), nasal obstruction (2), eyelid ptosis (1)
Anorectal	Rectorrhagia (4), tumor mass prolapse (2), anemia (2)
Urogenital	Tumor mass (6), pigmentation of external genitalia (1), vaginal bleeding (1)

n= number(s)

in 46.3% of cases while only 2 patients with urogenital melanomas were treated with RT.

Survival data: Overall survival (OS), expressed as a median value, was longer in urogenital melanomas (26 months), than sinonasal melanomas (14 months) and anorectal melanomas (6 months).

As reported in the Kaplan-Meier estimate (Figure 2), sinonasal and anorectal melanoma carried higher mortality in the first two years; anorectal melanoma had a high mortality rate over time while sinonasal melanoma reached a plateau. Urogenital melanoma showed longer survival in the first two years from diagnosis with delayed mortality.

The 24-month overall survival rate among mucosal melanoma patients was 54%. The 24-month overall mortality for the location was 37% in sinonasal melanomas, 18% in anorectal melanoma and 100% in urogenital melanoma. The last observed exit from the estimate was 58 months (Figure 2).

The univariate analysis showed that metastasis at diagnosis was significantly associated with mortality (Table 2). In the multivariate analysis, the risk factor significantly associated with mortality was the presence of metastasis at diagnosis, while first-line immunotherapy demonstrated a protective role (Table 4).

Histopathologic and Molecular Data

Mucosal melanomas can occur in all sites where mucosal melanocytes are present. While perianal, genital, and perioral skin normally harbors melanocytes (and, consequently, these are sites of origin of benign and malignant melanocytic tumors, albeit rare), melanocytes are usually absent in the bladder mucosa. In the rare case of bladder melanoma, a spread of melanocytes from the urethra could explain its etiopathogenesis. In the nasal and paranasal cavities, melanocytes can be found both in the epithelium and in the stroma, mainly in the dark-skinned population.

Delayed site-related detection of these melanomas can explain their architecture, which is often nodular or polypoid, and, at the same time, their thickness, which is usually higher than most cutaneous melanomas.

Most mucosal melanomas are often associated with an *in situ* lateral spread on the mucosal surface (Figure 3), which is a supportive feature that the tumor is primitive. Cytologically, mucosal melanomas are remarkably variable; neoplastic cells can be spindle, rhabdoid, epithelioid, small, or giant pleomorphic (often multinucleated), thus causing challenging diagnostic problems in differentiating them from lymphomas, carcinomas or sarcomas. Necrotic areas are frequent and mitotic activity is usually high (Figure 4). Due to their heterogeneous appearance, immunohistochemical staining (S100, MART-1, HMB45 or SOX10) is often required to demonstrate the melanocytic origin of the neoplasm.

In our series, epithelioid features were prevalent (25 out of 33 cases). Two cases were composed of spindle hyperpigmented cells, two cases had a lymphocytic-like appearance, one was rhabdoid and, in three cases, the cytological pattern of growth was mixed (Figure 5).

Mean Breslow thickness in mucosal melanoma was 6.7 with no appreciable difference between different anatomical sites; no Breslow thickness was reported in sinonasal melanomas due to the sparse and fragmented nature of biopsy specimens. Tumor ulceration was noted in 11 samples. In one case of vulvar melanoma, a residual melanocytic nevus was found at the periphery of the tumor.

No samples undergoing biomolecular analysis had BRAF or NRAS mutation, while 3 cases had c-KIT and 3 cases KRAS mutations.

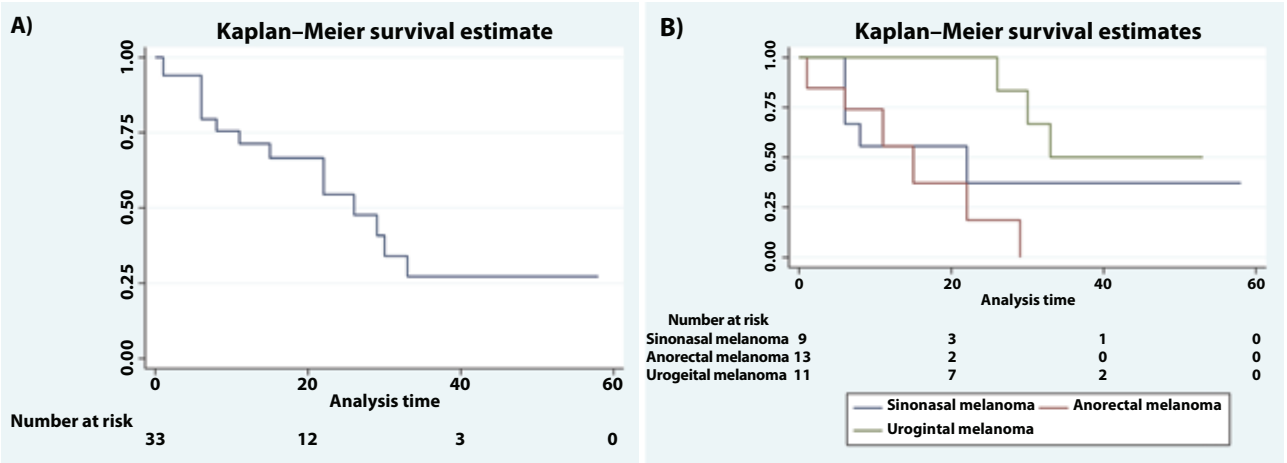

Figure 2. Kaplan Meier estimates for overall survival. (A) OS in mucosal melanomas. (B) Stratification of the cohort by the site of the primary tumor.

Table 3. Univariable model of risk factors for mortality in mucosal melanomas.

	HR 95% CI	p-value
Age at diagnosis	1.02 (0.97-1.07)	0.292
Gender		
Female	ref.	
Male	1.93 (0.67-5.45)	0.216
Location		
Sinonasal	ref.	
	1.90 (0.57-6.29)	0.291
Urogenital	0.25 (0.05-1.09)	0.066
Metastasis at diagnosis		
No	ref.	
Yes	8.75 (1.79-42.76)	**0.007**
Site of metastasis at diagnosis		
Skin/regional lymph node	ref.	
Visceral	3.30 (0.34-31.96)	0.302
Cerebral	6.21 (0.53-72.00)	0.144
≥2 sites	2.50 (0.22-27.95)	0.456
Surgery		
No	ref.	
Debulking	0.19 (0.02-1.59)	0.129
Radical	0.33 (0.09-1.16)	0.085
First-line biological therapy		
No	ref.	
Nivolumab	0.88 (0.26-2.95)	0.840
Pembrolizumab	1.16 (0.13-9.63)	0.890
Imatinib	2.71 (0.31-23.21)	0.362
First-line chemotherapy		
No	ref.	
Yes	1.84 (0.23-14.66)	0.561
Second-line systemic therapy		
No	ref.	
Ipilimumab	0.71 (0.09-5.68)	0.752
Pembrolizumab--		
Dacarbazine	1.42 (0.17-11.30)	0.740
Cytoreductive-palliative radiation therapy		
No	ref.	
Yes	1.65 (0.56-4.90)	0.360

HR: hazard ratio
CI: confidence interval

Detailed descriptive data from histopathologic and molecular data are reported in Table 5.

Discussion

This 11-year retrospective study shows that mucosal melanoma is a tumor typically arising in the older population, with a median age of 82, not significantly influenced by site of origin [13]. Demographic data also confirm that mucosal melanoma has a higher prevalence in females [9]; this result is largely driven by cases of vulvovaginal melanoma in the urogenital melanoma subgroup. Surprisingly, we have no records of oral cavity mucosal melanomas, which alone have been described as the second most frequent location in the head and neck region [2,8,9].

Histologically, most cases were made by epithelioid cells, regardless of the site of origin. In many cases, pleomorphic

Table 4. Multivariable model of risk factors for mortality in mucosal melanomas.

	HR 95% CI	p-value
Age at diagnosis	1.02 (0.96-1.09)	0.574
Gender		
Female	ref.	
Male	3.33 (0.98-11.25)	0.107
Metastasis at diagnosis		
No	ref.	
Yes	26.55 (3.18-221.42)	**0.001**
First-line biological therapy		
No	ref.	
Nivolumab	0.10 (0.01-0.75)	**0.025**
Pembrolizumab	0.04 (0.01-0.91)	**0.044**
Imatinib	0.09 (0.0-2.02)	0.133

CI: confidence interval

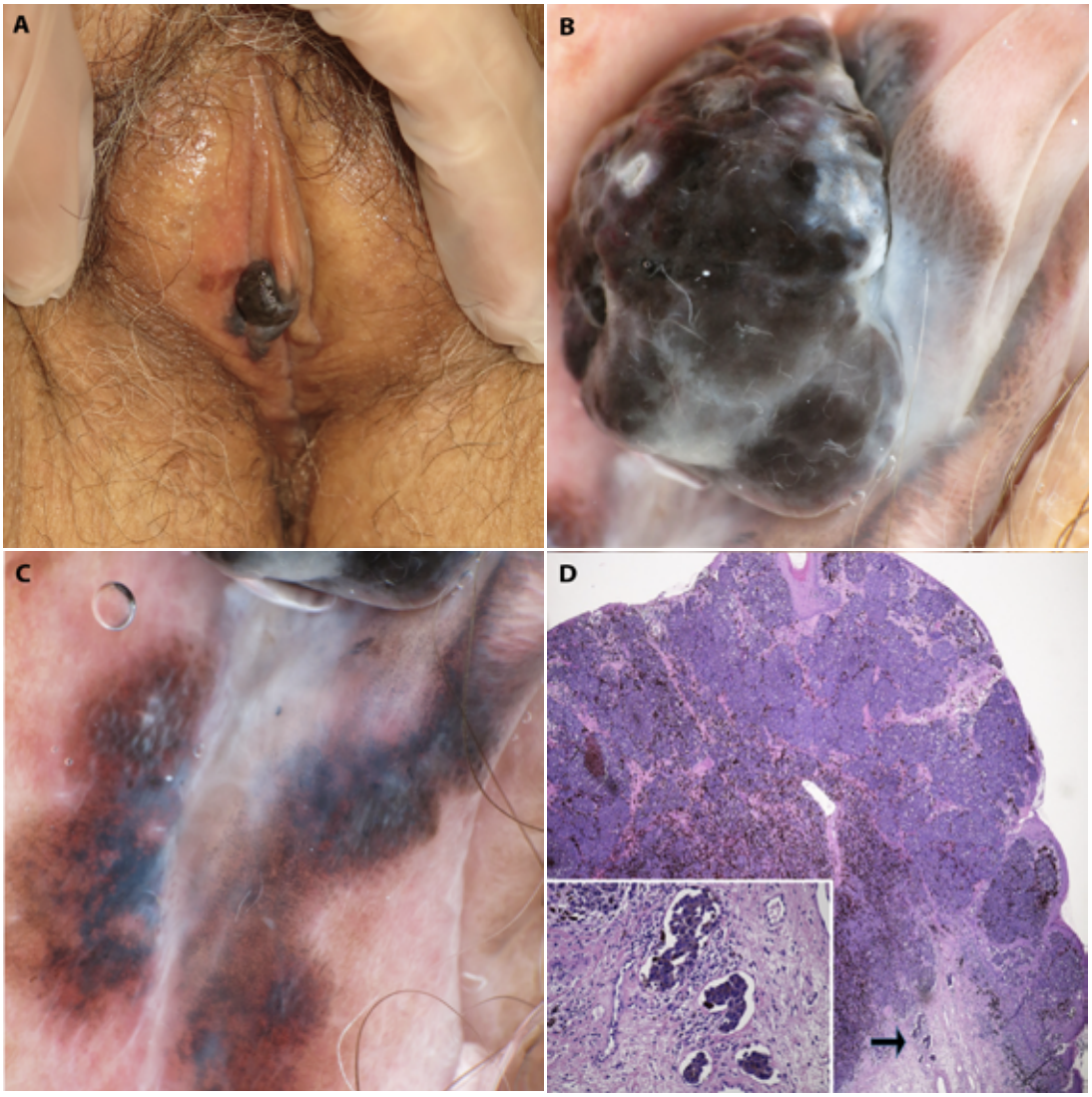

Figure 3. Vulvar melanoma (A) Clinical overview of a nodular hyperpigmented lesion of the vulva. (B) Dermoscopy of the nodular part shows a blue-black structureless area with shiny white structures and negative pigment network at the implant base. (C) Dermoscopy of the flat part shows blue and black globules and blotches, a blue-white veil, and shiny white structures. (D) Histology: the neoplasm is largely ulcerated, shows discrete necrotic areas, and reaches 11 mm thickness according to Breslow. At a higher power view, vascular invasion of neoplastic cells is visible (arrow).

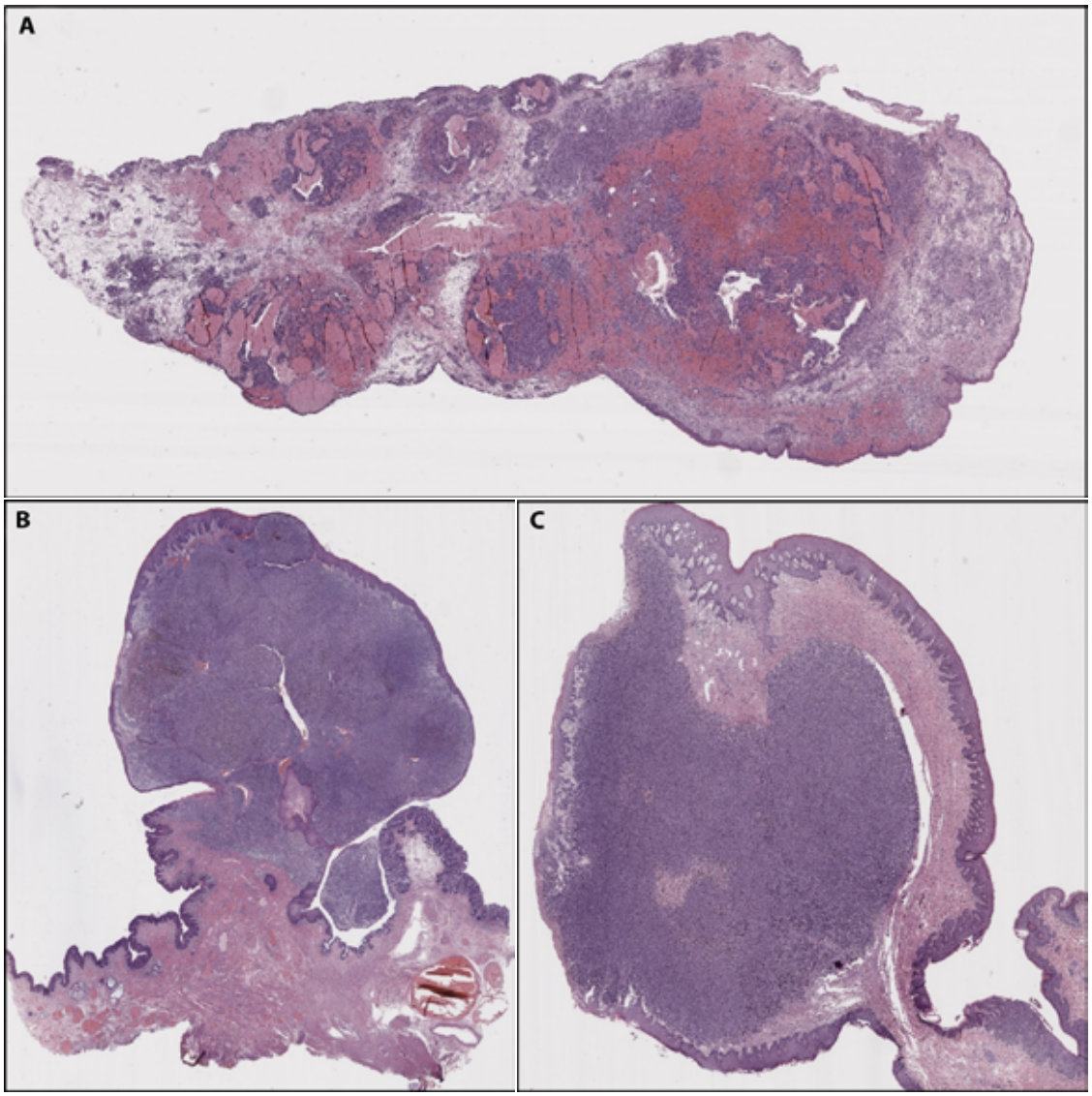

Figure 4. Architectural features of mucosal melanoma in hematoxylin and eosin. (A) A sinonasal melanoma growing as a polypoid, edematous, and highly vascularized mass. Melanoma involves the entire polyp with multiple confluent nodules, reaching at least 1 mm Breslow thickness. The transitional respiratory epithelium is still recognizable all around. (B) A nodular melanoma arising at the interface between intestinal and squamous perianal epithelium. Breslow thickness is 14 mm (C) A vaginal nodular melanoma without any visible in situ component in the squamous vaginal epithelium. The tumor is superficially ulcerated, and Breslow thickness is 9 mm.

areas with bizarre, giant cells were present. Only two cases of spindle cell melanomas were recorded, even if spindle cell areas occurred in three cases with a mixed pattern of growth. The epithelioid features and the presence of melanin, which in rare cases can be massive, simplified the diagnosis; *vice versa*, differential diagnosis resulted challenging in two cases of lymphoma-like melanoma (one anorectal and one genital) and an immunohistochemical panel of stains was necessary to rule out a lymphoproliferative process.

More than half of mucosal melanomas (54.4%) manifested with metastasis at diagnosis. Patients who were discovered with metastasis have an increased HR for death as highlighted by univariate analysis (Table 3); in addition, the prognostic value of metastatic status at diagnosis was reported by the multivariate model. These findings corroborate the evidence that diagnosing advanced-stage tumors has a relevant influence on prognosis [14]. As previously discussed [9], the site of origin of neoplasia, mostly anatomically occult, is a relevant cause of late diagnosis. Incidence of mucosal melanomas in older age could be an additional cause, as older people can delay seeking physician consultation.

The multivariate model also showed that the administration of immunotherapy as a first-line treatment was a protective factor for death, with a statistical significance both for nivolumab and pembrolizumab. No significance has been obtained for imatinib, because of the small sample.

It is interesting to highlight that, despite the small sample size in the current study, our data support the utility of

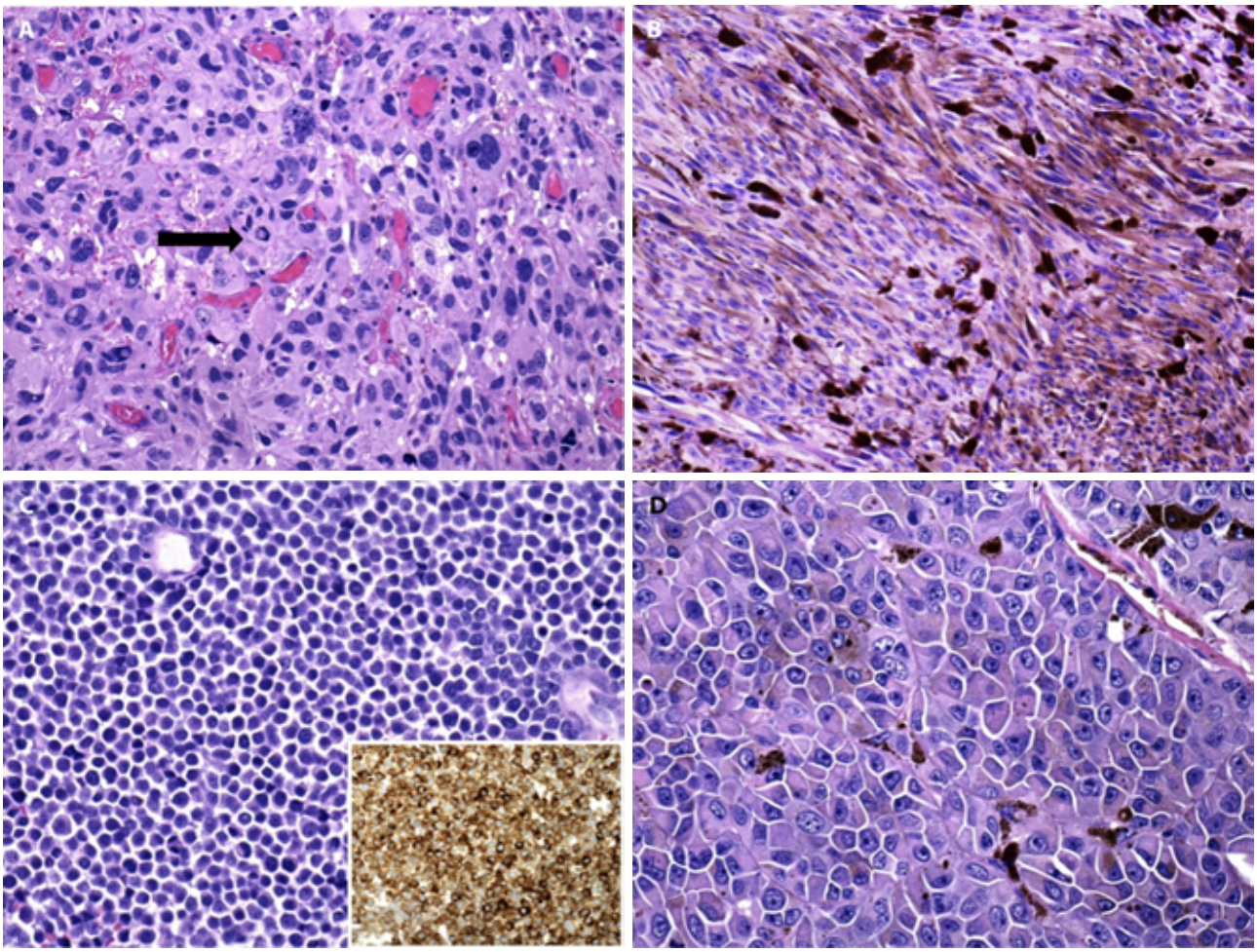

Figure 5. Unusual cytological features of mucosal melanoma in hematoxylin and eosin. (A) Pleomorphic areas in an epithelioid vulvar melanoma. Melanocytes are irregularly shaped, and nuclei are bizarre. The arrow indicates an abnormal mitotic figure. (B) A hyperpigmented genital melanoma, composed of middle-sized, mitotically active spindle cells. (C) A rectal melanoma made up of small, monomorphous lymphocytic-like cells. Immunohistochemical staining is necessary to confirm the melanocytic origin of the tumor (in the inset, HMB45 diffusely stains the cells). (D) A rectal melanoma with a rhabdoid appearance. Neoplastic cells show a large, eosinophilic cytoplasm and peripherally located round nucleus.

immunotherapy to prolong survival in metastatic mucosal melanoma [7]. A recent international cohort study [15] remarked on the efficacy of the anti-PD1 agent in prolonging survival in metastatic patients, even though to a lesser extent than in cutaneous melanoma. In fact, mucosal melanoma has been reported to have a lower expression of PD-L1 than its cutaneous counterpart [16] and of being more tolerogenic [17] probably because of the absent mutagenic role of UV radiation that prevents a high tumor mutational load and immunogenicity.

Urogenital Melanoma

In our series, urogenital melanoma showed 4 cases of metastasis in locoregional lymph nodes and no distant metastasis at diagnosis. Moreover, urogenital melanoma is the subgroup with the longer OS, with full survival at 24 months and decreased survival only after 26 months (Figure 2). The absence at diagnosis of disseminated disease is probably the most relevant factor that influences cohort survival. It was also reported [18,19] that females diagnosed with mucosal melanomas have higher survival, unrelated to the site of origin; thus, the longer survival in this cohort could also be driven by the prevalence of vulvovaginal melanoma in the subgroup. Surgical treatment with radical intent, undergone by all patients with urogenital melanoma in our series, may be an additional factor influencing longer survival.

No case of male urogenital melanomas was reported in the database of the Pathology Unit of our hospital confirming that mucosal melanoma of the male genital tract is a very rare occurrence [4].

Urogenital melanomas in our database manifested as a vegetating mass, new pigmentation of the external genitalia, or urogenital bleeding (Table 2).

Anorectal Melanoma

Patients with anorectal melanoma showed a younger age at diagnosis (Table 1).

Table 5. Mucosal melanoma pathological data and stratification by the site of origin.

	Mucosal melanomas (n=33, 100%)	Sinunasal (n=9, 27.3%)	Anorectal (n=13, 39.4%)	Urogenital (n=11, 33.3%)
Breslow, n, mean ± SD (range)	10, 6.7 ±5.2 (0.6-17)	-	3, 7.1 ±5.3 (1.4-12)	7, 6.5 ±5.6 (0.6-17)
Ulceration				
No	1 (3.0)	0 (0.0)	0	1 (9.1)
Yes	11 (33.3)	0 (0.0)	5 (38.5)	6 (54.5)
Cytology				
Epithelioid cells	25 (75.7)	9 (100)	10 (76.9)	6 (54.5)
Spindle cells	2 (6.1)	0 (0.0)	1 (7.6)	1 (9.1)
Small cells	2 (6.1)	0 (0.0)	1 (7.6)	1 (9.1)
Rhabdoid cells	2 (6.1)	0 (0.0)	1 (7.6)	0 (0.0)
Mixed	3 (9.1)	0 (0.0)	0 (0.0)	3 (27.2)
LVI				
No	7 (21.2)	1 (11.1)	1 (7.7)	5 (45.5)
Yes	5 (15.2)	1 (11.1)	2 (15.4)	2 (18.2)
BRAF, wt	25 (75.8)	8 (88.9)	10 (76.9)	7 (63.6)
c-KIT				
V560D	3 (9.1)	0 (0.0)	1 (7.7)	2 (18.2)
wt	8 (24.2)	2 (22.2)	5 (38.5)	1 (9.1)
NRAS, wt	9 (27.3)	3 (33.3)	4 (30.8)	2 (18.2)
KRAS				
p.A146V	1 (3.0)	0 (0.0)	1 (7.7)	0 (0.0)
p.G12A	1 (3.0)	1 (11.1)	0 (0.0)	0 (0.0)
p.G12C	1 (3.0)	0 (0.0)	1 (7.7)	0 (0.0)
wt	1 (3.0)	1 (11.1)	0 (0.0)	0 (0.0)

LVI: lymphovascular invasion

Even though all patients surgically managed in this subgroup underwent a radical intent procedure, Kaplan-Meier analysis showed the worst survival. This result is consistent with previous reports [15,18]. It is reasonable to suppose that a more widespread metastatic disease at diagnosis in this subgroup is the reason for this difference (Table 1). It was demonstrated that anorectal melanoma has an intrinsically aggressive behavior because of the high propensity to develop distant and brain metastases [18]; in our series, this subgroup is the only one manifesting with 2 cases of cerebral metastasis and with 3 cases of multiple visceral metastases at diagnosis.

Anorectal melanomas diagnosed in our clinics had presenting symptoms such as rectal bleeding, anemia, and prolapse of the tumor mass (Table 2).

Sinonasal Melanoma

In the sinonasal region, Breslow thickness is not easy to apply because of biopsy sampling. In fact, all surgical treatments proposed to this cohort of patients were debulking procedures that usually prevent obtaining a well-oriented full-thickness specimen for histopathological analysis.

Additional evidence emerging from Kaplan-Meier analysis is that the mortality of sinonasal mucosal melanomas was higher in the first 24 months and then decreased, reaching a plateau (Figure 2). Factors that may influence this behavior, such as radiation therapy, administered to all cohort patients, are still unclear and need to be further analyzed in a larger sample.

Sinonasal melanomas in our series manifested with epistaxis, nasal obstruction, and one case of eyelid ptosis (Table 2).

Conclusions

In conclusion, different strategies have to be developed to avoid late diagnosis; so far, there are no targeting campaigns or specific advice that can help physicians from different specialties (i.e. gynecologists) to get early diagnoses of this rare melanoma subsets. As promising results, the use of immunotherapy might impact the natural history of mucosal melanomas in improving overall or disease-free survival.

References

1. Broit N, Johansson PA, Rodgers CB. Meta-Analysis and Systematic Review of the Genomics of Mucosal Melanoma. *Mol Cancer Res MCR*. 2021;19(6):991-1004. doi:10.1158/1541-7786.MCR-20-0839. PMID: 33707307
2. López F, Rodrigo JP, Cardesa A. Update on primary head and neck mucosal melanoma. *Head Neck*. 2016;38(1):147-155. doi:10.1002/hed.23872. PMID: 25242350.
3. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer*. 1998;83(8):1664-1678. doi:10.1002/(sici)1097-0142(19981015)83:8<1664::aid-cncr23>3.0.co;2-g. PMID: 9781962
4. Mihajlovic M, Vlajkovic S, Jovanovic P, Stefanovic V. Primary mucosal melanomas: a comprehensive review. *Int J Clin Exp Pathol*. 2012;5(8):739-753. doi:.
5. Spencer KR, Mehnert JM. Mucosal Melanoma: Epidemiology, Biology and Treatment. *Cancer Treat Res*. 2016;167:295-320. doi:10.1007/978-3-319-22539-5_13
6. Yde SS, Sjoegren P, Heje M, Stolle LB. Mucosal Melanoma: a Literature Review. *Curr Oncol Rep*. 2018;20(3):28. doi:10.1007/s11912-018-0675-0. PMID: 29569184.
7. Li J, Kan H, Zhao L, Sun Z, Bai C. Immune checkpoint inhibitors in advanced or metastatic mucosal melanoma: a systematic review. *Ther Adv Med Oncol*. 2020;12:1758835920922028. doi:10.1177/1758835920922028. PMID: 32489431.
8. Linee guida melanoma AIOM 2021. AIOM. Published September 23, 2021. Updated January 2022. Accessed January 2022./https://www.aiom.it/linee-guida-aiom-2021-melanoma/
9. Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. *J Am Acad Dermatol*. 2007;56(5):828-834. doi:10.1016/j.jaad.2006.06.017. PMID: 17349716.
10. Seth R, Messersmith H, Kaur V, et al. Systemic Therapy for Melanoma: ASCO Guideline. *J Clin Oncol Off J Am Soc Clin Oncol*. 2020;38(33):3947-3970. doi:10.1200/JCO.20.00198. PMID: 32228358.
11. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2019;381(16). doi:10.1056/NEJMoa1910836. PMID: 31562797.
12. NCCN Guidelines Version 3.2022 Melanoma: Cutaneous. Updated April 2022. Accessed July 2022. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
13. Gutiérrez-Castañeda LD, Nova JA, Tovar-Parra JD. Frequency of mutations in BRAF, NRAS, and KIT in different populations and histological subtypes of melanoma: a systemic review. *Melanoma Res*. 2020;30(1):62-70. doi:10.1097/CMR.0000000000000628. PMID: 31274706.
14. Kuk D, Shoushtari AN, Barker CA, et al. Prognosis of Mucosal, Uveal, Acral, Nonacral Cutaneous, and Unknown Primary Melanoma From the Time of First Metastasis. *The Oncologist*. 2016;21(7):848-854. doi:10.1634/theoncologist.2015-0522
15. Dimitriou F, Namikawa K, Reijers ILM, et al. Single-agent anti-PD-1 or combined with ipilimumab in patients with mucosal melanoma: an international, retrospective, cohort study. *Ann Oncol Off J Eur Soc Med Oncol*. Published online June 16, 2022:S0923-7534(22)01731-8. doi:10.1016/j.annonc.2022.06.004. PMID: 35716907.
16. Kaunitz GJ, Cottrell TR, Lilo M, et al. Melanoma subtypes demonstrate distinct PD-L1 expression profiles. *Lab Investig J Tech Methods Pathol*. 2017;97(9):1063-1071. doi:10.1038/labinvest.2017.64. PMID: 28737763.
17. Goldemberg DC, Thuler LCS, de Melo AC. An Update on Mucosal Melanoma: Future Directions. *Acta Dermatovenerol Croat ADC*. 2019;27(1):11-15. doi:.
18. Heppt MV, Roesch A, Weide B, et al. Prognostic factors and treatment outcomes in 444 patients with mucosal melanoma. *Eur J Cancer Oxf Engl 1990*. 2017;81:36-44. doi:10.1016/j.ejca.2017.05.014. PMID: 28600969.
19. Cinotti E, Chevallier J, Labeille B, et al. Mucosal melanoma: clinical, histological and c-kit gene mutational profile of 86 French cases. *J Eur Acad Dermatol Venereol JEADV*. 2017;31(11):1834-1840. doi:10.1111/jdv.14353