Management of Noncutaneous Melanomas

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KEYWORDS

• Mucosal melanoma • Anorectal melanoma • Vulvovaginal melanoma
• Head and neck mucosal melanoma • Sinonasal melanoma

KEY POINTS

- Noncutaneous melanoma is associated with poor overall survival rates and high rates of metastatic disease.
- Mucosal melanomas are amelanotic in one-third to one-half of cases, which can cause difficulty in making the initial diagnosis.
- Elective nodal dissection is not recommended for mucosal melanoma. There is a paucity of data to support use of sentinel lymph node biopsy.
- Mucosal melanomas have overall higher rates of KIT mutations but much lower rates of BRAF mutations compared with cutaneous melanoma.

INTRODUCTION

Mucosal melanoma is a rare subtype of melanoma that represents only 1.3% of all melanoma cases[1] and has distinct clinical, biological, and management considerations compared with cutaneous melanoma. Unlike the dramatic and steady increase in the incidence of cutaneous melanoma, mucosal melanoma incidence rates have remained steady.[2] Furthermore, unlike cutaneous melanoma, there are no known risk factors for developing mucosal melanoma and there is no known association with sun exposure. However, most mucosal melanomas present with advanced-stage disease, possibly explained by the lack of early symptoms as well as the mucosal locations being less accessible to routine screening. Approximately one-third to one-half of patients with mucosal melanoma have nodal involvement at the time of presentation,[3,4] and the prognosis is generally very poor, with 5-year overall survival rates of approximately 25%.[3] Even for patients with localized disease, survival in patients with mucosal melanoma was significantly worse than for patients with

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cutaneous melanoma (10%–60% for various mucosal sites vs >90% for cutaneous),[2] suggesting a true difference in the biology of the two entities. The proximity of these tumors to other vital organs often makes local control challenging, and the rarity of this disease makes clinical trials, and even consistent data, difficult to achieve. Data and treatment options are often extrapolated from cutaneous melanoma, but it is not clear that this is appropriate.

Patients with mucosal melanoma tend to present in their 50s to 80s, with median age at presentation in the 60s (**Table 1**). Mucosal melanomas tend to occur near mucocutaneous junctions, with the most common sites being head and neck (55.4%), anorectal (23.8%), and vulvovaginal (18.0%).[3,5] Although mucosal melanoma has a slight female predominance with a female/male ratio of 1.85:1,[1] this is likely skewed by the frequency of vulvovaginal melanomas, which do not have a male counterpart. Different sites of mucosal melanoma have different incidence patterns by race and sex. Altieri and colleagues[4] performed a review of the population-based California Cancer Registry from 1988 to 2013 and found that, although mucosal melanoma only represented 1% of melanomas in non-Hispanic white people, it accounted for 15% of melanomas in Asian/Pacific Islanders, 9% of melanomas in non-Hispanic black people, and 4% of melanomas in Hispanic people. They also found that anorectal mucosal melanomas were most common in female Asian/Pacific Islanders, whereas head and neck mucosal melanomas were most common among Hispanic people and genitourinary mucosal melanomas were most common in non-Hispanic white people.

This article discusses clinicopathologic features, staging, and management of locoregional disease for the 3 most common sites: head and neck, anorectal, and vulvovaginal. Because there is a paucity of site-specific data regarding available systemic therapy, this is covered in a more global sense in relation to mutational analysis and systemic therapy for mucosal melanoma at the end of this article.

Ocular melanoma accounts for approximately 3.7% of melanoma cases[1] and also has a distinct pattern of management compared with either mucosal or cutaneous melanoma. The diagnosis and primary tumor management of ocular melanoma is highly specialized and typically performed by an ophthalmic oncologist and not by a general surgical oncologist. Therefore, its management is not discussed in this article. The exceptions to this are regional therapies for ocular melanoma liver metastases, which are reviewed in an article on regional therapies elsewhere in this issue.

HEAD AND NECK MUCOSAL MELANOMA

Clinical Features, Staging, and Prognosis

Head and neck mucosal melanomas most commonly occur in the sinonasal region (up to two-thirds) followed by the oral cavity.[2,6] The most common presenting symptoms for sinonasal melanoma are epistaxis and nasal obstruction.[7] Oral cavity mucosal melanomas are most often asymptomatic and detected by the patient or on oral examination. There are some reports of preceding oral melanosis,[8] but there is no clear evidence that this represents a premalignant state. Because approximately half of all head and neck mucosal melanomas are amelanotic,[9] the primary tumor is not always distinguishable on examination from other tumors of the head and neck. Confirmation with a panel of standard markers for melanoma such as S100, melan-A, tyrosinase, and/or HMB45 is helpful to confirm the diagnosis.[9] Oral cavity melanomas are more likely than sinonasal melanomas to present with cervical nodal involvement (25% vs 6%)[6] and clinicians should routinely examine all patients for the presence of cervical lymphadenopathy. Standard work-up should include a complete history and physical, including endoscopic examination plus computed tomography (CT) and/or

Table 1
Clinicopathologic features of the most common sites of mucosal melanoma versus cutaneous melanoma

	Cutaneous Melanoma	Head and Neck Melanoma	Anorectal Melanoma	Vulvovaginal Melanoma
Incidence (per million)[1]	153.5	0.7	0.4	1
Median Age at Diagnosis (y)	63	61	68–71	63
Male/Female Predilection	Slight male predominance	Slight male predominance for oral cavity	1.6-fold higher in women	Female predominance
Presence of Amelanosis (%)	1.8–8	50	29–71	27
Staging Systems Used	AJCC cutaneous melanoma	AJCC head and neck mucosal melanoma Ballantyne 3-tier staging	AJCC cutaneous melanoma Ballantyne 3-tier staging	AJCC cutaneous melanoma Ballantyne 3-tier staging FIGO (cervical)
5-y Overall Survival (%)	89	All 25 Sinonasal 38	17	Vulvar 20–54 Vaginal 10–32
Common Mutations				
BRAF (%)	41–52	3.5–8	10	0–26
c-KIT (%)	3	5–9.5	24–33	18–22
NRAS (%)	18–28	0–4.8 (30 in sinonasal)	19	4–12
Other (%)	—	—	NF1 (20)	—

Abbreviations: AJCC, American Joint Commission on Cancer; FIGO, International Federation of Gynecology and Obstetrics; NF1, neurofibromatosis type 1.

MRI with contrast to define the anatomy of the primary tumor. PET/CT and/or CT scan of the chest/abdomen/pelvis and brain MRI may be considered in more advanced cases.[10]

Head and neck mucosal melanomas are the only mucosal melanomas that are represented in the eighth edition of the American Joint Commission on Cancer (AJCC) staging manual (**Table 2**).[11] Because of the aggressiveness of these lesions, the lowest T category that can be assigned is T3, in which tumors are limited to the mucosa and immediately underlying soft tissue. T4a represents tumors that involve deep soft tissue, cartilage, bone, or overlying skin, and T4b represents tumors that involve brain, dura, lower cranial nerves (IX–XII), masticator space, carotid artery, prevertebral space, or mediastinal structures. The regional lymph node (N) and distant metastasis (M) categories are dichotomized into the presence or absence of regional nodal metastases or distant metastases, respectively. Although the T, N, and M categories remain defined and are prognostic,[12] in the eighth edition of the AJCC staging manual the overall prognostic stage grouping was eliminated. An alternative staging criteria, which are used in other mucosal melanomas, is the 3-tier Ballantyne staging, in which stage I represents clinically localized disease, stage II represents regional lymph node disease, and stage III represents distant disease[13] (**Table 3**). Overall 5-year survival is

Table 2
Tumor, node, metastasis definitions for head and neck mucosal melanoma

Category	Criteria
T (Primary Tumor)	
T3	Tumor limited to mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension; eg, polypoid nasal disease and pigmented or nonpigmented lesions of the oral cavity, pharynx, or larynx
T4a	Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, or overlying skin
T4b	Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures
N (Regional Lymph Node)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present
M (Distant Metastasis)	
M0	No distant metastasis
M1	Distant metastasis present
Prognostic stage grouping: There is currently no proposed prognostic stage grouping	

Adapted from Amin MB, American Joint Committee on Cancer., American Cancer Society. AJCC cancer staging manual. Eight edition / editor-in-chief, Mahul B. Amin, MD, FCAP ; editors, Stephen B. Edge, MD, FACS and 16 others ; Donna M. Gress, RHIT, CTR - Technical editor ; Laura R. Meyer, CAPM - Managing editor. ed. Chicago IL: American Joint Committee on Cancer, Springer; 2017.

poor, ranging from 25% to 38%.[14–16] In retrospective studies, older age, anatomic site in the nasopharynx and paranasal sinuses, and presence of distant metastatic disease have all been associated with worse prognosis.[6,14,15] Studies have been mixed as to whether primary tumor thickness is associated with survival, which may suggest that thickness in some instances just reflects extent of local tumor invasion. Similarly, nodal disease has not always been associated with survival. The primary cause of therapeutic failure is distant metastasis.[17]

Surgical Management

When feasible, the National Comprehensive Cancer Network (NCCN) guidelines recommend surgical excision of the primary site followed by adjuvant radiation for T4a and high-risk T3 disease.[10] Because major resections in the head and neck region can be very morbid and type of surgery has not been shown to correlate with rates of distant metastasis or death, there has been a move toward less aggressive resections and more endoscopic resections.[7,18] For general surgical oncologists, these cases

Table 3
Ballantyne 3-tier staging for mucosal melanoma

Stage	Description
I	Localized disease
II	Regional nodal disease
III	Distant metastatic disease

should be undertaken with surgeons who have sufficient head and neck experience as well as plastic surgeons to assist in reconstruction, when appropriate. Patients with documented T4b disease are not recommended to have surgery, but instead should get primary radiation and/or systemic therapy versus a clinical trial (preferred, if available).

Although sentinel lymph node biopsy is feasible and reported case series suggest that there may be prognostic value to performing sentinel lymph node biopsy,[19,20] because of the paucity of data it is not recommended as a routine part of surgical management or staging. For sinonasal melanoma, there is a lower incidence of lymph node metastases, and a large retrospective study from MD Anderson found that lymph node status was not a significant predictor of outcome.[21] Therefore, elective lymph node dissection for sinonasal melanoma is not recommended and therapeutic lymph node dissections should only be done in the setting of clinically positive lymph nodes. Because oral cavity melanoma is associated with higher rates of nodal metastases, the role of elective neck dissection is less clear. The most recent NCCN guidelines do include neck dissection in the management algorithm for oral cavity melanomas that are clinically node negative, but this is not based on prospective data.[10]

Radiation Therapy

Adjuvant radiation in head and neck mucosal melanoma can improve locoregional control[7,17,22–25] and is recommended in the NCCN guidelines for T4a and strongly considered for T3 lesions. However, it has not been shown to have any survival benefit.[7,22,25] Patients with locally advanced, unresectable disease are candidates for definitive radiation to the primary tumor and high-risk lymph node basins.[10,23]

ANORECTAL MUCOSAL MELANOMA

Clinical Features, Staging, and Prognosis

Anorectal melanoma accounts for approximately 0.4% to 1.1% of all melanoma cases.[26,27] According to a Surveillance, Epidemiology, and End Results (SEER) database study, the median age at presentation is 71 years and there is a 1.6-fold higher incidence in women than in men.[28] The transitional zone of the anal canal contains melanocytes, which increase from the dentate line to the anoderm. However, melanocytes have also been shown to be present above the dentate line in the colorectal zone,[29] and both anal-based and rectal-based mucosal melanomas have been described. Because many of these occur at the mucocutaneous border, it can sometimes be unclear whether anal melanomas are of cutaneous origin or mucosal origin. Common presenting symptoms include bleeding, pain, pruritus, and a mass.[26,30] Similar to head and neck mucosal melanomas, diagnosis can be delayed because of high rates of amelanosis (29%–71%)[30–32] and these lesions may be mistaken for other, more common, benign anorectal conditions such as hemorrhoids or rectal polyps. Immunohistochemistry staining with S100, HMB-45, and Mart-1/Melan-A is helpful in confirming the diagnosis.[33] Initial work-up should include digital rectal examination and anoscopy/endoscopy for evaluation of extent of local disease as well as either PET/CT or CT of the chest, abdomen, and pelvis to rule out distant metastatic disease. Addition of pelvic MRI (**Fig. 1**) can be useful in determining the extent of local invasion as well as regional nodal disease, and brain MRI can be considered in advanced cases to rule out brain metastases.

Unlike head and neck mucosal melanoma, there are no AJCC staging criteria for anorectal melanoma. Although there are no standard staging criteria, the 3-tier Ballantyne staging is often used when stage I represents clinically localized disease, stage II

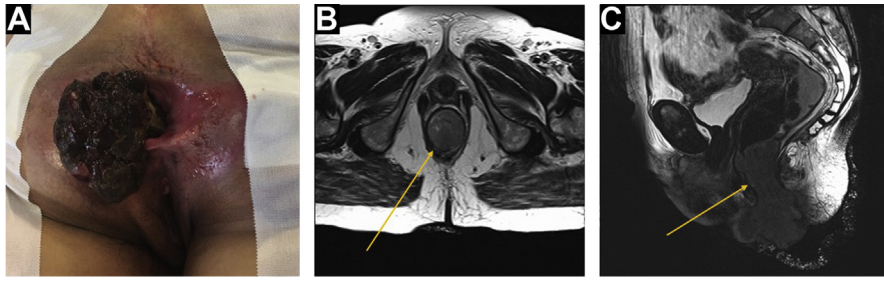

Fig. 1. Rectal melanoma with a long stalk and bulky disease extending past the anal canal on physical examination (*A*) and pelvic MRI (*B, C; arrows*).

represents regional lymph node disease, and stage III represents distant disease[13] (see **Table 3**). One study from MD Anderson studied 160 anorectal melanomas and found that the eighth edition AJCC cutaneous melanoma staging system was able to risk stratify patients with anorectal melanoma,[34] and is therefore used by some clinicians for staging. Primary tumor characteristics, including primary tumor thickness and lymphovascular invasion, correlated with disease-specific survival in patients with localized or regional disease but not with those who presented with distant metastases (with a universally poor prognosis). Up to a third of patients can present with metastatic disease[35] and overall 5-year survival is poor, ranging from 16% to 31%.[2,31,36,37] In retrospective studies, higher stage, presence of lymph node metastases, tumor thickness, amelanotic melanomas, and perineural invasion[26,34,36,38,39] have been associated with a worse prognosis.

Surgical Management

For patients with nonmetastatic disease, surgical excision remains the cornerstone of treatment. Historically, more aggressive surgical approaches, including abdominoperineal resection (APR) for anorectal melanoma, was the standard of care. However, many retrospective studies comparing the outcomes of APR with wide local excision have shown no difference in survival,[32,37,39] likely because there is a high rate of distant metastasis regardless of primary tumor surgical procedure. Therefore, if technically feasible, local excision with or without adjuvant radiation is preferred, with the ultimate goal of obtaining negative histologic margins (R0). In 1 retrospective study, R0 resection was associated with improved 5-year survival compared with patients with positive margins regardless of type of surgical approach (19% vs 6%, $P<.001$).[40] There have not been prospective trials investigating various clinical margins in mucosal melanoma. Use of at least a 1-cm margin with 1-cm to 2-cm margins for thicker lesions would be appropriate, although the risks and benefits of taking a larger margin must be carefully considered when additional margin is likely to result in additional morbidity. In particular, when assessing patients with bulky rectal melanomas, these can sometimes be attached to a smaller area of mucosa and extend with a stalk and therefore be amenable to local excision despite their bulky nature (see **Fig. 1**). The use of digital rectal examination, anoscopy/endoscopy, and MRI can be helpful in determining the best surgical approach. Although there is greater morbidity and additional quality-of-life issues associated with an APR, it still should be considered a treatment option for patients with localized bulky or recurrent disease.

The anorectal region has 2 potential lymphatic drainage patterns. Tumors can drain via the mesenteric nodes to the hypogastric and para-aortic nodes, or they can drain

to the superficial inguinal lymph nodes. All potential draining nodal basins should be assessed by imaging and physical examination. Although there are case reports showing the technical feasibility of sentinel lymph node biopsy,[41–43] there is insufficient evidence to draw a conclusion about the prognostic or therapeutic value of the procedure, and there is currently no defined role for sentinel lymph node biopsy in anorectal melanoma. Given the variability in drainage patterns and high rates of distant metastasis, elective lymph node dissection is also not recommended. However, in the setting of clinically evident lymph node disease and in the absence of distant metastases, therapeutic lymph node dissection is recommended to gain regional control.

Radiation Therapy

Use of adjuvant radiation therapy in conjunction with sphincter-preserving local excision has been shown to be well tolerated and provide good local control but has not been associated with any improvement in overall survival.[36,44] Inclusion of inguinal nodal basins in the radiation field was not associated with improved outcome but did result in increased lymphedema.[44] Data are sparse on the use of primary radiation for treatment of anorectal melanoma. There are small case series in which patients do have temporary palliation of symptoms and it can be considered for selected patients with advanced disease or who are not surgical candidates.[45,46]

VULVOVAGINAL MUCOSAL MELANOMA

Clinical Features, Staging, and Prognosis

The 2 primary types of mucosal melanoma in the female genital tract are vulvar melanoma and vaginal melanoma. They both present with a median age in the 60s, but the range for vulvar melanomas is wider, with patients as young as 10 years old reported.[47] The most common presenting symptoms are pain, bleeding, pruritus, and/or a lesion/lump.[48,49] Approximately one-third of vulvovaginal melanomas are amelanotic and can be confused for other gynecologic lesions.[50,51] Dermoscopy may aid in differentiating melanoma from other pigmented vulvovaginal lesions.[52] Once biopsied, immunohistochemistry staining with a panel of S-100, HMB-45, Melan-A, tyrosinase, and MART-1 is helpful to confirm the diagnosis.[53] Standard work-up should include a pelvic examination and CT, MRI, and/or ultrasonography of the groin and pelvis to assess for locoregional disease (**Fig. 2**). In clinically suspected advanced cases, PET/CT and brain MRI may be used to rule out distant metastatic disease.

Similar to anorectal mucosal melanoma, there is no separate AJCC staging for vulvovaginal melanoma. The 3-tier Ballantyne staging used for other mucosal melanomas can be applied, in which stage I represents clinically localized disease, stage II represents regional lymph node disease, and stage III represents distant disease[13] (see **Table 3**). Previously, the AJCC staging for cutaneous melanoma has been applied to vulvar and vaginal melanomas and was shown to be prognostic.[54,55] Therefore, it is used by most treating physicians for vulvar and vaginal melanomas. In addition, some physicians have used the International Federation of Gynecology and Obstetrics (FIGO) 4-tier staging system used in other gynecologic malignancies, although this is primarily for cervical melanomas, which are very rare. Overall 5-year survival for vulvar melanomas ranges from 20% to 54%, and is worse for vaginal melanomas, approximately 10% to 32%.[50,56–59] Clinical features associated with worse prognosis include older age, regional nodal or distant disease, increased Breslow thickness, higher AJCC stage, and amelanosis.[47,49,54,60–62] Although the clitoral area and labia majora are the most common sites for vulvar melanoma,[63] centrally located vulvar lesions tend to be at higher risk of nodal involvement.[54]

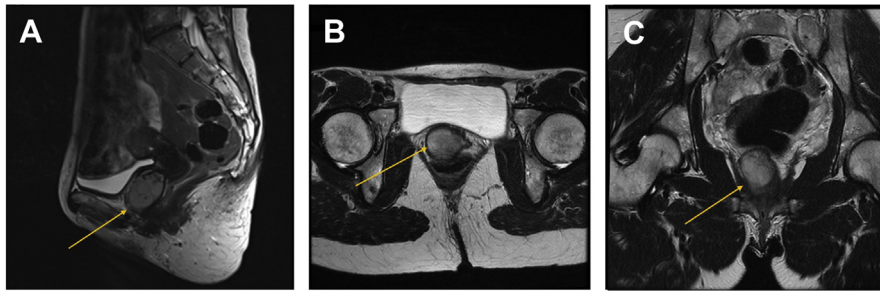

Fig. 2. (*A–C*) Pelvic MRI showing bulky vaginal melanoma (*arrows*) contained within the vaginal canal.

Surgical Management

Surgery is the cornerstone of treatment of primary vulvovaginal melanoma. Similar to anorectal melanoma, wide local excision and radical vulvectomy/pelvic exenteration have similar survival rates,[47,56,61] and therefore, when feasible, local excision is the preferred primary surgical treatment. There are no robust data regarding appropriate margins for local excision, but at least a 1-cm deep margin and 1-cm to 2-cm circumferential margin based on thickness and adjacent critical structures are generally recommended.[59,64]

Vaginal melanoma is similar to anorectal melanoma in its variable lymphatic drainage patterns, with drainage potentially to inguinal basins, pelvic basins, or both. There is a paucity of data regarding sentinel lymph node biopsy for vaginal melanomas and therefore no specific recommendations have been made.[59,64] In contrast with vaginal melanomas, sentinel lymph node biopsy for vulvar melanoma has been shown to be accurate and feasible, and it has been recommended by the Gynecologic Cancer Intergroup (GCIG) consensus review that patients with at least 1-mm thick vulvar melanomas undergoing wide local excision also be considered for a sentinel lymph node biopsy,[59,64,65] recognizing that there are few data compared with cutaneous melanoma. Elective lymph node dissection in patients with clinically negative regional nodal basins is not recommended. Regardless of primary site, patients with clinically positive lymph nodes without distant metastatic disease should undergo therapeutic lymph node dissection with the aim of improving locoregional control.

Radiation Therapy

Retrospective data have not shown any associated benefit of adjuvant radiation in vulvovaginal melanoma and it is therefore not routinely recommended.[47,58,64] A case series of 4 patients receiving ipilimumab with concurrent external beam radiation showed a favorable tumor response, with 1 having a complete pathologic response on pathologic review of the resection specimen.[66] Further studies combining radiation with checkpoint blockade are needed to validate these promising results.

MUTATIONAL ANALYSIS AND SYSTEMIC THERAPY FOR MUCOSAL MELANOMA

Because of the rarity of mucosal melanomas, there are few prospective studies for systemic therapy designed specifically for mucosal melanomas. Systemic therapy used in cutaneous melanoma has been extrapolated to use in mucosal melanoma, but generally with poor survival outcomes. Advanced cases of mucosal melanoma have been treated with cytotoxic chemotherapy in the past, but with a modest response rate to first-line therapy of about 10%.[67] A 3-arm phase II randomized trial

of adjuvant high-dose interferon-α2b versus temozolomide plus cisplatin versus observation in Asian patients with resected mucosal melanoma showed that both regimens were safe and had better overall and recurrence-free survival compared with surgery alone.[68] Temozolomide plus cisplatin had longer median overall survival (48.7 vs 40.4 months) and longer median recurrence-free survival (20.8 months vs 9.4 months) compared with interferon. Exploratory subgroup analysis suggested that the benefit was mostly for head and neck mucosal melanomas.

More recently, attention has been drawn to potential use of targeted inhibitors and immunotherapy for mucosal melanoma. Overall, mucosal melanomas have a different genomic profile (see **Table 1**)[69–73] than cutaneous melanoma, which is associated with ultraviolet (UV) radiation exposure. As a whole, mucosal melanomas have an increased rate of c-KIT mutations (39%)[74] relative to cutaneous melanoma (~3%), but this is mostly caused by increased frequency in anorectal and vulvovaginal melanomas, not head and neck melanomas. For these patients, c-KIT inhibitors such as imatinib may be useful for patients with metastatic disease,[8,74–77] but development of imatinib resistance may limit the ability to have a durable response even in patients with imatinib-sensitive mutations.[78] Although BRAF mutations are fairly common in cutaneous melanoma (41%–52% of all cases, but higher in areas of chronic sun damage), they are rare in mucosal melanoma (~11% overall). In addition, many of the BRAF mutations documented are not the V600E mutation often seen in cutaneous melanoma.[79–81] However, patients with BRAF mutations may still respond to BRAF/MEK inhibitors, and should still be routinely included in the mutational analysis panel. NRAS mutations are overall less frequent in mucosal melanoma compared with cutaneous melanoma. However, among the mucosal melanomas, NRAS mutations have been shown to occur more frequently in anorectal[34] and sinonasal melanomas[82] and may be responsive to MEK inhibition, although the type of mutation alone has not been shown to have any prognostic value.

Some patients with mucosal melanoma were included in prospective randomized trials with immune checkpoint blockade. Retrospective review of the mucosal melanoma cohort treated in published prospective trials or as a part of an expanded access program found a 23% response rate to single-agent nivolumab or pembrolizumab, and 37% to combination ipilimumab with nivolumab.[83,84] However, progression-free survival was only 3 months and 6 months respectively, suggesting a continued need for effective systemic therapy for mucosal melanoma. A recent phase 1 clinical trial of an anti–programmed cell death protein 1 (PD-1) antibody (toripalimab) combined with an anti–vascular endothelial growth factor (VEGF) antibody (axitinib) found that, in an Asian population with metastatic mucosal melanoma, the combination was tolerable and resulted in objective responses in 14 of 29 (48%) chemotherapy-naive patients.[85] These data require validation in a larger cohort and with a non-Asian population as well.

SUMMARY

Mucosal melanoma is a rare disease with no identifiable risk factors. It has been difficult to standardize treatment of mucosal melanomas because of the rarity of the disease, a paucity of prospective data, and the lack of a uniformly accepted staging system. Overall prognosis is poor for all mucosal melanomas. Patients are more likely to present with advanced disease compared with cutaneous melanoma, which may be caused by lack of early symptoms and high rates of amelanosis (25%–70%) compared with cutaneous melanoma (1.8%–8%),[86,87] which adds to the difficulty in distinguishing melanoma from other more common, benign diseases.

Surgical management has moved toward wide local excision (when feasible) instead of more radical procedures. This shift in surgical approach is the result of the high likelihood of systemic failure regardless of extent of primary tumor surgery, and therefore no difference in overall survival outcomes based on type of surgery. Although therapeutic lymph node dissection for clinically evident disease is considered standard, there is a paucity of data regarding the utility of sentinel lymph node biopsy. Elective lymph node dissection has largely been abandoned.

Mutational analysis shows that mucosal melanomas differ from the usual UV radiation–associated changes seen in cutaneous melanoma, with mucosal melanomas having lower rates of BRAF mutation and higher rates of c-KIT mutations. Appropriate mutational analysis is important in advanced cases in which systemic therapy may be warranted. Although there is no clear best systemic therapy, the use of immunotherapy and/or targeted inhibitors shows some promise, and further clinical trials in this area will be of great interest to clinicians managing this disease.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. McLaughlin CC, Wu XC, Jemal A, et al. Incidence of noncutaneous melanomas in the U.S. Cancer 2005;103(5):1000–7.
2. Bishop KD, Olszewski AJ. Epidemiology and survival outcomes of ocular and mucosal melanomas: a population-based analysis. Int J Cancer 2014;134(12): 2961–71.
3. Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. J Am Acad Dermatol 2007;56(5):828–34.
4. Altieri L, Wong MK, Peng DH, et al. Mucosal melanomas in the racially diverse population of California. J Am Acad Dermatol 2017;76(2):250–7.
5. 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):1664–78.
6. Patel SG, Prasad ML, Escrig M, et al. Primary mucosal malignant melanoma of the head and neck. Head Neck 2002;24(3):247–57.
7. Moreno MA, Roberts DB, Kupferman ME, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M. D. Anderson Cancer Center. Cancer 2010;116(9):2215–23.
8. Seetharamu N, Ott PA, Pavlick AC. Mucosal melanomas: a case-based review of the literature. Oncologist 2010;15(7):772–81.
9. Williams MD. Update from the 4th edition of the World Health Organization classification of head and neck tumours: mucosal melanomas. Head Neck Pathol 2017;11(1):110–7.
10. NCCN clinical practice guidelines in oncology: head and neck cancers, version 3.2019. 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed September 17, 2019.
11. Amin MB, Edge S, Greene s, et al. In: AJCC cancer staging manual. 8th edition. Chicago: American Joint Committee on Cancer, Springer; 2017.
12. Koivunen P, Back L, Pukkila M, et al. Accuracy of the current TNM classification in predicting survival in patients with sinonasal mucosal melanoma. Laryngoscope 2012;122(8):1734–8.

13. Ballantyne AJ. Malignant melanoma of the skin of the head and neck. An analysis of 405 cases. Am J Surg 1970;120(4):425–31.
14. Jethanamest D, Vila PM, Sikora AG, et al. Predictors of survival in mucosal melanoma of the head and neck. Ann Surg Oncol 2011;18(10):2748–56.
15. Amit M, Tam S, Abdelmeguid AS, et al. Patterns of treatment failure in patients with sinonasal mucosal melanoma. Ann Surg Oncol 2018;25(6):1723–9.
16. Bachar G, Loh KS, O'Sullivan B, et al. Mucosal melanomas of the head and neck: experience of the Princess Margaret Hospital. Head Neck 2008;30(10):1325–31.
17. Liu ZP, Luo JW, Xu GZ, et al. Failure patterns and prognostic factors of patients with primary mucosal melanoma of the nasal cavity and paranasal sinuses. Acta Otolaryngol 2017;137(10):1115–20.
18. Hanna E, DeMonte F, Ibrahim S, et al. Endoscopic resection of sinonasal cancers with and without craniotomy: oncologic results. Arch Otolaryngol Head Neck Surg 2009;135(12):1219–24.
19. Prinzen T, Klein M, Hallermann C, et al. Primary head and neck mucosal melanoma: Predictors of survival and a case series on sentinel node biopsy. J Craniomaxillofac Surg 2019;47(9):1370–7.
20. Starek I, Koranda P, Benes P. Sentinel lymph node biopsy: A new perspective in head and neck mucosal melanoma? Melanoma Res 2006;16(5):423–7.
21. Amit M, Tam S, Abdelmeguid AS, et al. Approaches to regional lymph node metastasis in patients with head and neck mucosal melanoma. Cancer 2018;124(3):514–20.
22. Li W, Yu Y, Wang H, et al. Evaluation of the prognostic impact of postoperative adjuvant radiotherapy on head and neck mucosal melanoma: a meta-analysis. BMC Cancer 2015;15:758.
23. Trotti A, Peters LJ. Role of radiotherapy in the primary management of mucosal melanoma of the head and neck. Semin Surg Oncol 1993;9(3):246–50.
24. Meleti M, Leemans CR, de Bree R, et al. Head and neck mucosal melanoma: experience with 42 patients, with emphasis on the role of postoperative radiotherapy. Head Neck 2008;30(12):1543–51.
25. Samstein RM, Carvajal RD, Postow MA, et al. Localized sinonasal mucosal melanoma: Outcomes and associations with stage, radiotherapy, and positron emission tomography response. Head Neck 2016;38(9):1310–7.
26. Wanebo HJ, Woodruff JM, Farr GH, et al. Anorectal melanoma. Cancer 1981;47(7):1891–900.
27. DeMatos P, Tyler DS, Seigler HF. Malignant melanoma of the mucous membranes: a review of 119 cases. Ann Surg Oncol 1998;5(8):733–42.
28. Cote TR, Sobin LH. Primary melanomas of the esophagus and anorectum: epidemiologic comparison with melanoma of the skin. Melanoma Res 2009;19(1):58–60.
29. Clemmensen OJ, Fenger C. Melanocytes in the anal canal epithelium. Histopathology 1991;18(3):237–41.
30. Chiu YS, Unni KK, Beart RW Jr. Malignant melanoma of the anorectum. Dis Colon Rectum 1980;23(2):122–4.
31. Brady MS, Kavolius JP, Quan SH. Anorectal melanoma. A 64-year experience at Memorial Sloan-Kettering Cancer Center. Dis Colon Rectum 1995;38(2):146–51.
32. Ward MW, Romano G, Nicholls RJ. The surgical treatment of anorectal malignant melanoma. Br J Surg 1986;73(1):68–9.
33. Balachandra B, Marcus V, Jass JR. Poorly differentiated tumours of the anal canal: a diagnostic strategy for the surgical pathologist. Histopathology 2007;50(1):163–74.

34. Nagarajan P, Piao J, Ning J, et al. Prognostic model for patient survival in primary anorectal mucosal melanoma: stage at presentation determines relevance of histopathologic features. Mod Pathol 2020;33(3):496–513.
35. Thibault C, Sagar P, Nivatvongs S, et al. Anorectal melanoma–an incurable disease? Dis Colon Rectum 1997;40(6):661–8.
36. Ballo MT, Gershenwald JE, Zagars GK, et al. Sphincter-sparing local excision and adjuvant radiation for anal-rectal melanoma. J Clin Oncol 2002;20(23):4555–8.
37. Iddings DM, Fleisig AJ, Chen SL, et al. Practice patterns and outcomes for anorectal melanoma in the USA, reviewing three decades of treatment: is more extensive surgical resection beneficial in all patients? Ann Surg Oncol 2010; 17(1):40–4.
38. Pessaux P, Pocard M, Elias D, et al. Surgical management of primary anorectal melanoma. Br J Surg 2004;91(9):1183–7.
39. Yeh JJ, Shia J, Hwu WJ, et al. The role of abdominoperineal resection as surgical therapy for anorectal melanoma. Ann Surg 2006;244(6):1012–7.
40. Nilsson PJ, Ragnarsson-Olding BK. Importance of clear resection margins in anorectal malignant melanoma. Br J Surg 2010;97(1):98–103.
41. Sanli Y, Turkmen C, Kurul S, et al. Sentinel lymph node biopsy for the staging of anal melanoma: report of two cases. Ann Nucl Med 2006;20(9):629–31.
42. Olsha O, Mintz A, Gimon Z, et al. Anal melanoma in the era of sentinel lymph node mapping: a diagnostic and therapeutic challenge. Tech Coloproctol 2005; 9(1):60–2.
43. Damin DC, Rosito MA, Spiro BL. Long-term survival data on sentinel lymph node biopsy in anorectal melanoma. Tech Coloproctol 2010;14(4):367–8.
44. Kelly P, Zagars GK, Cormier JN, et al. Sphincter-sparing local excision and hypofractionated radiation therapy for anorectal melanoma: a 20-year experience. Cancer 2011;117(20):4747–55.
45. Harwood AR, Cummings BJ. Radiotherapy for mucosal melanomas. Int J Radiat Oncol Biol Phys 1982;8(7):1121–6.
46. Bujko K, Nowacki MP, Liszka-Dalecki P. Radiation therapy for anorectal melanoma–a report of three cases. Acta Oncol 1998;37(5):497–9.
47. Sugiyama VE, Chan JK, Shin JY, et al. Vulvar melanoma: a multivariable analysis of 644 patients. Obstet Gynecol 2007;110(2 Pt 1):296–301.
48. Wechter ME, Gruber SB, Haefner HK, et al. Vulvar melanoma: a report of 20 cases and review of the literature. J Am Acad Dermatol 2004;50(4):554–62.
49. Boer FL, Ten Eikelder MLG, Kapiteijn EH, et al. Vulvar malignant melanoma: Pathogenesis, clinical behaviour and management: Review of the literature. Cancer Treat Rev 2019;73:91–103.
50. Ragnarsson-Olding B, Johansson H, Rutqvist LE, et al. Malignant melanoma of the vulva and vagina. Trends in incidence, age distribution, and long-term survival among 245 consecutive cases in Sweden 1960-1984. Cancer 1993;71(5): 1893–7.
51. An J, Li B, Wu L, et al. Primary malignant amelanotic melanoma of the female genital tract: report of two cases and review of literature. Melanoma Res 2009; 19(4):267–70.
52. Murzaku EC, Penn LA, Hale CS, et al. Vulvar nevi, melanosis, and melanoma: an epidemiologic, clinical, and histopathologic review. J Am Acad Dermatol 2014; 71(6):1241–9.
53. Gupta D, Malpica A, Deavers MT, et al. Vaginal melanoma: a clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Pathol 2002;26(11): 1450–7.

54. Phillips GL, Bundy BN, Okagaki T, et al. Malignant melanoma of the vulva treated by radical hemivulvectomy. A prospective study of the Gynecologic Oncology Group. Cancer 1994;73(10):2626–32.
55. Wechter ME, Reynolds RK, Haefner HK, et al. Vulvar melanoma: review of diagnosis, staging, and therapy. J Low Genit Tract Dis 2004;8(1):58–69.
56. DeMatos P, Tyler D, Seigler HF. Mucosal melanoma of the female genitalia: a clinicopathologic study of forty-three cases at Duke University Medical Center. Surgery 1998;124(1):38–48.
57. Pleunis N, Schuurman MS, Van Rossum MM, et al. Rare vulvar malignancies; incidence, treatment and survival in the Netherlands. Gynecol Oncol 2016;142(3):440–5.
58. Kirschner AN, Kidd EA, Dewees T, et al. Treatment approach and outcomes of vaginal melanoma. Int J Gynecol Cancer 2013;23(8):1484–9.
59. Gadducci A, Carinelli S, Guerrieri ME, et al. Melanoma of the lower genital tract: Prognostic factors and treatment modalities. Gynecol Oncol 2018;150(1):180–9.
60. Ragnarsson-Olding BK, Nilsson BR, Kanter-Lewensohn LR, et al. Malignant melanoma of the vulva in a nationwide, 25-year study of 219 Swedish females: predictors of survival. Cancer 1999;86(7):1285–93.
61. Trimble EL, Lewis JL Jr, Williams LL, et al. Management of vulvar melanoma. Gynecol Oncol 1992;45(3):254–8.
62. Seifried S, Haydu LE, Quinn MJ, et al. Melanoma of the vulva and vagina: principles of staging and their relevance to management based on a clinicopathologic analysis of 85 cases. Ann Surg Oncol 2015;22(6):1959–66.
63. Ragnarsson-Olding BK, Kanter-Lewensohn LR, Lagerlof B, et al. Malignant melanoma of the vulva in a nationwide, 25-year study of 219 Swedish females: clinical observations and histopathologic features. Cancer 1999;86(7):1273–84.
64. Leitao MM Jr, Cheng X, Hamilton AL, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for vulvovaginal melanomas. Int J Gynecol Cancer 2014;24(9 Suppl 3):S117–22.
65. Trifiro G, Travaini LL, Sanvito F, et al. Sentinel node detection by lymphoscintigraphy and sentinel lymph node biopsy in vulvar melanoma. Eur J Nucl Med Mol Imaging 2010;37(4):736–41.
66. Schiavone MB, Broach V, Shoushtari AN, et al. Combined immunotherapy and radiation for treatment of mucosal melanomas of the lower genital tract. Gynecol Oncol Rep 2016;16:42–6.
67. Shoushtari AN, Bluth MJ, Goldman DA, et al. Clinical features and response to systemic therapy in a historical cohort of advanced or unresectable mucosal melanoma. Melanoma Res 2017;27(1):57–64.
68. Lian B, Si L, Cui C, et al. Phase II randomized trial comparing high-dose IFN-alpha2b with temozolomide plus cisplatin as systemic adjuvant therapy for resected mucosal melanoma. Clin Cancer Res 2013;19(16):4488–98.
69. Lyu J, Wu Y, Li C, et al. Mutation scanning of BRAF, NRAS, KIT, and GNAQ/GNA11 in oral mucosal melanoma: a study of 57 cases. J Oral Pathol Med 2016;45(4):295–301.
70. Ozturk Sari S, Yilmaz I, Taskin OC, et al. BRAF, NRAS, KIT, TERT, GNAQ/GNA11 mutation profile analysis of head and neck mucosal melanomas: a study of 42 cases. Pathology 2017;49(1):55–61.
71. Yang HM, Hsiao SJ, Schaeffer DF, et al. Identification of recurrent mutational events in anorectal melanoma. Mod Pathol 2017;30(2):286–96.
72. Hou JY, Baptiste C, Hombalegowda RB, et al. Vulvar and vaginal melanoma: A unique subclass of mucosal melanoma based on a comprehensive molecular

analysis of 51 cases compared with 2253 cases of nongynecologic melanoma. Cancer 2017;123(8):1333–44.
73. Aulmann S, Sinn HP, Penzel R, et al. Comparison of molecular abnormalities in vulvar and vaginal melanomas. Mod Pathol 2014;27(10):1386–93.
74. Curtin JA, Busam K, Pinkel D, et al. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 2006;24(26):4340–6.
75. Rivera RS, Nagatsuka H, Gunduz M, et al. C-kit protein expression correlated with activating mutations in KIT gene in oral mucosal melanoma. Virchows Arch 2008; 452(1):27–32.
76. Dumaz N, Andre J, Sadoux A, et al. Driver KIT mutations in melanoma cluster in four hotspots. Melanoma Res 2015;25(1):88–90.
77. Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol 2013;31(26):3182–90.
78. Postow MA, Hamid O, Carvajal RD. Mucosal melanoma: pathogenesis, clinical behavior, and management. Curr Oncol Rep 2012;14(5):441–8.
79. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med 2005;353(20):2135–47.
80. Lee JH, Choi JW, Kim YS. Frequencies of BRAF and NRAS mutations are different in histological types and sites of origin of cutaneous melanoma: a meta-analysis. Br J Dermatol 2011;164(4):776–84.
81. Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. Cell 2015;161(7):1681–96.
82. Amit M, Tam S, Abdelmeguid AS, et al. Mutation status among patients with sinonasal mucosal melanoma and its impact on survival. Br J Cancer 2017;116(12): 1564–71.
83. Shoushtari AN, Munhoz RR, Kuk D, et al. The efficacy of anti-PD-1 agents in acral and mucosal melanoma. Cancer 2016;122(21):3354–62.
84. D'Angelo SP, Larkin J, Sosman JA, et al. Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol 2017;35(2):226–35.
85. Sheng X, Yan X, Chi Z, et al. Axitinib in combination with toripalimab, a humanized immunoglobulin G4 monoclonal antibody against programmed cell death-1, in patients with metastatic mucosal melanoma: an open-label phase IB trial. J Clin Oncol 2019;37(32):2987–99.
86. Thomas NE, Kricker A, Waxweiler WT, et al. Comparison of clinicopathologic features and survival of histopathologically amelanotic and pigmented melanomas: a population-based study. JAMA Dermatol 2014;150(12):1306–14.
87. Koch SE, Lange JR. Amelanotic melanoma: the great masquerader. J Am Acad Dermatol 2000;42(5 Pt 1):731–4.