REVIEW

Update on primary mucosal melanoma

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Mucosal melanomas are aggressive cancers of mucosal surfaces with clinical and pathologic characteristics distinct from cutaneous melanomas, warranting different staging systems and treatment approaches. Surgical resection is performed frequently for the primary tumor, although the utility of lymph node surgery and radiation therapy is not established. Therapies targeted against C-KIT activating mutations, identified in many mucosal melanomas, are emerging as promising treatments. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.03.031.)

Key words: anorectal mucosal melanoma; C-KIT inhibitors; clinical characteristics; mucosal melanoma of the head and neck; pathology; urinary tract melanoma; vulvar and vaginal mucosal melanoma; treatment.

Primary mucosal melanomas (MMs) include head and neck, anorectal, vulvovaginal, and urinary tract melanomas, in order of frequency.[1] Between 1996 and 2000, the incidence rate per million was 1.2 for vulvar, 0.7 for head and neck, 0.4 for anorectal, 0.3 for vaginal, and 0.1 for penile MM, age-adjusted to the 2000 United States population, as reported to the North American Association of Central Cancer Registries.[2] These melanomas are often invasive when diagnosed and are associated with a poor prognosis.[3] Compared to cutaneous melanomas (CMs), MMs are rare, and the risk factors and etiology are not as well established.[2,4,5] In a recent study, patients with genital and anorectal MM were compared with those with CM; a family history of melanoma was a risk factor for both MM and CM, although it was more strongly associated with MM.[4] Interestingly, 6% of individuals with MM developed subsequent primary CM in that study.[4] Although ultraviolet radiation exposure is an important risk factor for CM, it has not been associated with the development of MM. MM and CM also appear to have different somatic mutation profiles; BRAF mutations are rare in MM, while activating mutations of the cell surface receptor tyrosine kinase (C-KIT) are identified more frequently.[6-8] Finally, CMs arise from the malignant transformation of melanocytes in the skin, of neural crest lineage; non-CMs are hypothesized to arise from melanoblasts

Abbreviations used:

AJCC:	American Joint Committee on Cancer
APR:	abdominoperineal resection
CM:	cutaneous melanoma
CSD:	chronic sun damage
C-KIT:	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
DSS:	disease-specific survival
MM:	mucosal melanoma
MMP:	mucosal melanomas of the penis
MMU:	primary urethral melanomas
MMAR:	mucosal melanomas of the anorectum
MMHN:	mucosal melanomas of the head and neck
MMVV:	mucosal melanomas of the vulva and vagina
OR:	overall response
OS:	overall survival
RT:	radiation therapy
SEER:	Surveillance, Epidemiology, and End Results
SLNB:	sentinel lymph node biopsy
TNM:	tumor, node, metastasis
WLE:	wide local excision

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migrating to noncutaneous organs after neural crest cells undergo an epithelial–mesenchymal transition.[5,9]

Available data on MM derive largely from retrospective studies. In this paper, clinical characteristics, staging, prognosis, pathology, and treatment of MMs by subtype will be reviewed.

MUCOSAL MELANOMAS OF THE HEAD AND NECK

MMs of the head and neck (MMHN) are rare tumors, accounting for 815 cases reported in the Surveillance, Epidemiology, and End Results (SEER) program between 1973 and 2007.[10] These patients had MMHN located in the nasal cavity, paranasal sinuses, oral cavity, and nasopharynx; most were women (53.9%) and white (87.9%), with a mean age at diagnosis of 68.7 years. In another study of 30 patients, nasal obstruction and epistaxis were the presenting symptoms in sinonasal melanomas, whereas oral cavity melanomas were frequently discovered by the patients or physicians as pigmented lesions (Fig 1).[11] Other symptoms of oral cavity melanomas were bleeding and tooth mobility.

Historically, MMHN was classified as local disease (stage I) with either regional metastasis (stage II) or distant metastasis (stage III), although this classification system is not uniformly used.[10,12-17] The American Joint Committee on Cancer (AJCC) published a dedicated staging system for MMHN based on the tumor, node, metastasis (TNM) classification similar to the staging system for CM; however, primary MMHN limited to the mucosa are considered T3 lesions to reflect their aggressive behavior.[3] Rare in situ MMs are excluded from staging. A retrospective analysis validated the AJCC stage and individual TNM status as appropriately predicting both disease-free and overall survival (OS).[18] The prognosis of MMHN is poor, with a 5-year OS of 25.2% in the SEER cohort of 815 cases, consistent with single-institution reports of 5-year OS ranging from 22% to 38%.[10,16,18] In the SEER cohort, factors that predicted a poorer prognosis included age >70 years, tumor size >2 cm, the presence of nodal metastases, the presence of distant metastases at diagnosis, and location in the nasopharynx and paranasal sinuses.[10] Although pathologic characteristics differed between oral cavity and sinonasal MMHN, there was no correlation with disease-specific survival (DSS) among patients treated in a US hospital (Table I).[11]

Locoregional control is attained with surgical resection of the primary tumor with or without lymph node dissection and/or radiation.[10,16-18,33] Aggressive surgical treatment of positive margins is indicated when feasible, though achieving clear margins may be difficult because of the proximity of critical anatomic structures.[18,34] The benefit of sentinel lymph node biopsy (SLNB) remains under investigation.[35-37] Local tumor resection with neck dissection for confirmed cervical lymph node metastases or of clinically and sonographically negative neck lymph nodes did not improve cumulative survival rates compared with local tumor resection alone.[38] However, neck dissection for clinically positive nodes is performed for local control of MMHN.[18] In 1 study, radiation therapy (RT) was given either as a primary treatment or after surgical excision in 55 MMHN patients with the intent to cure.[16] There was no difference in locoregional control between the 2 groups; however, 5-year OS was significantly worse in patients treated with primary RT. In addition, 1 report assessed 160 MMHN patients treated with surgery alone or surgery followed by adjuvant RT.[39] Those who received adjuvant RT had a significantly lower rate of locoregional recurrence, but there was no difference in relapse-free or OS.

CAPSULE SUMMARY

- Mucosal melanomas are aggressive tumors that are frequently treated with surgery.
- Mucosal melanomas often have different genetic aberrations than cutaneous melanomas.
- Mucosal melanomas should be assessed for the presence of C-KIT mutations; when detected, C-KIT inhibitors may be a therapeutic option.

MUCOSAL MELANOMAS OF THE ANORECTUM

MMs of the anorectum (MMAR) may be difficult to diagnose and mistaken for hemorrhoids, polyps, and anorectal cancer.[19,40] In a Swedish study of 251 patients with MMAR, the mean age at diagnosis was 71 years in men and 69 years in women, with a higher age-standardized incidence in women (1.0 per 10^6 women).[41] Among these patients, the most commonly affected areas included the anal canal and the anal canal/rectum overlapping or anal verge/perianal area (Fig 2). Among 40 patients in another study, rectal bleeding was the most common initial symptom; other presentations were a palpable anorectal mass, tenesmus, incontinence, inguinal mass, pruritus, weight loss, a change in bowel habits, and incidental findings during endoscopy.[19] There is