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Rare Presentations of Primary Melanoma and Special Populations: A Systematic Review

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Abstract

A subset of patients with melanoma present in rare and unique clinical circumstances requiring specific considerations with respect to diagnostic and therapeutic interventions. Herein we present

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our review of patients with: (1) primary mucosal melanoma of the head and neck, gastrointestinal and genitourinary tracts; (2) primary melanoma of the eye; (3) desmoplastic melanoma; (4) subungual melanoma; (5) melanoma in special populations: children, non-Caucasians, as well as a discussion of familial melanoma.

INTRODUCTION

Malignant melanoma can be a challenging malignancy, with rare and difficult to treat primary presentations. Herein we review recent updates in diagnostics and therapeutics in certain rare primary melanomas including special populations. Finally, we include a brief overview of familial melanoma syndrome and the role of certain genetic mutations and their impact on clinical practice.

Primary Mucosal Melanomas of the Head and Neck

Mucosal melanomas of the head and neck are a rare and aggressive variant of primary melanoma first described by Weber in 1856 and account for approximately 1% of all melanomas.[1,2] Two-thirds of lesions arise in the nasal cavity and paranasal sinuses, an additional one-quarter arise in the oral cavity, with the remainder occurring at other sites.[3] Unfortunately, because of the lack of visibility and relative asymptomatic nature of small lesions, mucosal melanoma of this region is often diagnosed at more advanced stages. Overall 5 year survival rates for this patient population is usually poor (<50%), with presentation usually 10-20 years later than cutaneous melanoma.[2,4,5] The presenting symptoms are usually epistaxis and/or nasal obstruction.

These melanomas generally present as polypoid lesions thereby making the primary lesion impossible to stage with the normal Breslow depth method. Traditionally these lesions were staged according to Ballantyne's clinical staging system.[6] In the American Joint Commission on Cancer (AJCC) 7th edition, mucosal melanomas of the head and neck are staged separately from other primary melanomas using a modified tumor, node, and metastasis (TNM) method. For instance, the primary tumor (T) is staged according to the amount of invasion of local structures,[3] while nodal involvement (N) is based solely on the presence or absence of metastatic spread to the regional nodes, without taking into account the size or number of lymph nodes involved. Finally metastatic spread (M) is based on the presence or absence of distant metastatic disease.

Histologic diagnosis of this subtype can be somewhat confusing, as in the case of an amelanotic lesion. Differential diagnoses often include inverting papilloma, carcinoma, and olfactory neuroblastoma.[7] The use of immunohistochemistry in diagnosis is invaluable in providing the correct diagnosis. As other tumors will stain for S-100 and/or Human Melanoma Black-45 (HMB-45), it is recommended that differential diagnosis of this melanoma subtype include additional melanoma specific staining, such as the use of Melan-A.[7] Additionally, these tumors rarely show mutation of BRAF V600E, however can show various mutations of c-KIT, which may provide a specific target for systemic therapy in a subgroup of patients.[4]

Given the lack of randomized controlled trials, treatment of this melanoma remains somewhat subjective. Surgical resection, with adequate margins, is the usual treatment of choice when there is local disease.[1,2,4,7] As many patients may present with locally advanced disease, full staging prior to surgical intervention is recommended. Because of the anatomic challenge that melanoma of this origin can pose, post-operative radiotherapy is usually recommended, especially for patients in which clear surgical margins are unable to be achieved, however given lack of randomized data, this remains highly individualized with varying outcomes.[1,2,4,7,8] Additionally the role of adjuvant immunotherapy/chemotherapy is even less clear. In general, patients with melanoma of mucosal origin have traditionally been excluded from clinical trials therefore outcomes with regard to adjuvant immunotherapy/chemotherapy are severely lacking and therefore highly individualized based on the treating provider's preference.

Gastrointestinal Melanoma

Although melanoma of the gastrointestinal tract is most commonly due to hematogenous dissemination of a cutaneous primary, it can rarely represent a primary melanoma. Primary gastrointestinal melanomas have been reported in the esophagus,[9] stomach,[10] small bowel,[11] colon,[12] and anorectum.[13-15] This unusual situation is identified clinically when there is no history of a primary cutaneous melanoma and no other evidence of disseminated disease. Histological support for a primary gastrointestinal melanoma includes an in-situ component and a radial growth phase of focal melanocytosis is often present. It is hypothesized that an alternative pathogenesis of gastrointestinal melanoma may exist and differ from that of primary cutaneous melanoma in that gastrointestinal melanoma may arise from schwannian neuroblast cells associated with the autonomic innervation of the gut,[16] melanocytic differentiation of neural crest cells which are found extensively in the intestine,[17] or may be due to neoplastic transformation of amine-precursor uptake and decarboxylation (APUD) cells within the gut.[11]

Given their location these primary lesions are often large and go un-diagnosed until symptomatic from obstruction or bleeding, consequently regional nodal metastases are present in 80% of patients.[9] The prognosis is worse than loco-regionally advanced primary cutaneous melanoma, but is better than traditional visceral metastatic disease. Making the distinction between primary and metastatic gastrointestinal disease is ideal but not always possible, as primary disease may warrant more aggressive locoregional surgical intervention, given the possibility for long-term survival.

Anorectal melanoma is an unusual form of primary mucosal melanoma that accounts for less than 1% of all melanoma subtypes.[18] In contrast to cutaneous melanoma, anal melanoma is rarely associated with BRAF mutations. However, studies demonstrate a subset of anal melanomas with KIT mutations, which may be susceptible to tyrosine kinase inhibitors.[19,20] Although more than 70% of patients present with localized disease, the majority will relapse with distant disease,[13] and, regardless of aggressive surgical treatment, the mean survival is only 2 years with 5-year overall survival rates around 20-30%.[14,21] Tumor size, necrosis and perineural invasion are poor histological features usually associated with recurrence and decreased survival.[15] The most important prognostic factor seems to be the ability to achieve

negative surgical margins[22] however, with no convincing evidence that an aggressive surgical approach improves local control or survival. Therefore, patients with localized disease should undergo sphincter-preserving wide local excision with a negative margin of 1-2 cm when possible. A more aggressive abdominoperineal resection should be reserved for palliation of localized bulky disease or for selected patients with local recurrence. Most tumors arise near or at the squamocolumnar junction in the anal canal and therefore drain to the superficial inguinal lymph nodes. Involvement of mesenteric lymph nodes, albeit rarely, usually reflects a localized presentation of systemic disease. Sentinel lymph node biopsy (SLNB) is a tool that can guide inguinal lymphatic treatment in order to avoid the morbidity of bilateral inguinal lymphadenectomy. While a negative SLNB will obviate the need for inguinal dissection, a positive SLNB can direct an inguinal lymphadenectomy to the select few who may benefit (resected primary, no evidence of distant metastatic disease and microscopic regional nodal involvement). As a result of the rarity of this disease, the logical approach to selective inguinal treatment has not undergone rigorous scrutiny. Regional nodal metastases do not carry the same prognostic significance as in cutaneous melanoma; however, resection of all clinically evident disease can result in long-term cure in a small subset of patients.[13-15] Because of the rarity of the disease and the fact that most patients relapse with distant disease, positron emission tomography (PET) imaging prior to surgical intervention is advised and enrollment in a clinical trial is encouraged.

Primary Vaginal/Vulvar Melanoma

Primary melanoma of the female genital tract is a rare presentation with incidence rates estimated at about 1/1,000,000 females annually and account for approximately 3-7% of all female melanomas.[23,24] Because of the general lack of accessibility and late presentation, prognosis is generally poor, with a 5-year survival rate of <50% for vulvar and <18% for vaginal melanomas.[25] Again noted is the extreme rare occurrence of BRAF mutations in the female genital tract variant.[26-28] However mutations in KIT (exons 11, 13, and 17) have been demonstrated in vulva/vagina melanoma and with commercially available agents targeted towards this mutation (i.e imatinib) may provide another target for treatment of metastatic disease in this population. [29,30]

Most patients present with the typical sequelae of vaginal bleeding, a palpable mass, discharge, itching, or asymptomatically with a pigmented lesion seen on routine examination. The usual treatment is surgery and can include wide local excision, vulvectomy, vaginectomy, or total exenteration depending on the ability to achieve clear margins. However, survival does not appear to be significantly improved with radical surgery; consequently, less invasive procedures should be pursued first if clear margins can be obtained.[24] Similar to anal melanoma as described above, SLNB can be performed to assess regional lymph node status and thus eliminates the need for inguinal lymphadenectomy if negative.[24,31,32]

Because of the general lack of randomized control trial data, the use of adjuvant therapy remains largely controversial and should be prescribed on an individual basis. Unfortunately the vast majority of patients will eventually have systemic dissemination and will thus require systemic therapy.

Primary Melanoma of the Eye

Melanoma of uveal origin has an incidence rate of approximately 5 to 7 new cases per 1 million persons per year.[33] Pathological staging is based mainly on the size of the mass, its location, and the presence or absence of metastases.

Iris melanoma is considerably less frequent than choroidal or ciliary body melanomas, usually with a better prognosis, with a lower potential for metastatic spread (approximately 3-5% risk)[34] and has a unique TNM staging system[3]. General presenting symptoms are a new or growing pigmented lesion seen on the iris, elevated intraocular pressure, and decreased vision.[35] As these can be relatively slow growing tumors with low risk of metastasis, patients can be serially observed, or in patients who are experiencing symptoms (i.e. recurrent hemorrhages, or glaucoma), treatment could include iris resection, plaque brachytherapy, or eye enucleation and are generally managed by specialized ophthalmologists unless metastases develop.[35,36]

Ciliary and choroidal melanomas tend to behave very similarly both from a pathological standpoint and metastatic potential. Both types of melanomas are classified according to tumor size based on the largest basal diameter and largest tumor thickness in 4 categories.[3] Ciliary and choroidal melanomas usually present with gradual visual loss and potentially pain. Diagnosis of these types of lesions is usually done based on physical findings, with biopsy not taking place until the time of definitive therapy (i.e brachytherapy, enucleation) Specifically when certain clinical and echographic findings are present the diagnostic accuracy is upwards of 99%.[36] Upon funduscopic exam, there may be a presence of a pigmented choroidal mass, which may appear like a dome or mushroom shape.[36] Treatment of these melanomas is achieved either through eye enucleation or I125 plaque brachytherapy. The Collaborative Ocular Melanoma Study (COMS) which randomized patients to one of the two treatments above demonstrated that there was no statistically significant difference in overall survival rates (81% vs 82% respectively P=.48).[37]

Traditionally the risk for metastasis has been the size, location and histopathologic type of the tumor.[38,39] More recently RNA-based gene-expression profiling of primary uveal melanomas has revealed two major subgroups with prognostic significance: class 1 (low metastatic risk) and class 2 (high metastatic risk).[40,41] However given the lack of available adjuvant treatments for uveal melanoma, this can only be used as a tool to help guide clinicians on issues of surveillance in this population. The liver is the most common initial site of metastasis in more than 90% of patients, and might be the only involved site. Therefore patients who are potentially considered high risk may benefit from, good history taking, physical exam, serial monitoring with liver imaging, and/or liver function tests, in an attempt to identify metastatic spread early on. Patients with limited disease to the liver can potentially be treated with liver directed therapy such as radio frequency ablation (RFA), stereotactic body radiotherapy (SBRT), transarterial chemotherapy embolization (TACE), hepatic artery embolization (HAE), or surgical resection. Whereas patients with diffuse liver or extrahepatic metastasis generally require systemic therapy, generally consists of the same regimens as those used to treat cutaneous metastatic melanoma. Additionally while BRAF mutations are exceedingly rare in uveal melanomas[42], there are certain patients whose

tumors will exhibit mutations of either KIT or GNAQ[29,43,44] , which may offer potential other targets of systemic therapy.

Desmoplastic Melanoma

Desmoplastic melanoma (DM) is a rare but histologically and clinically distinct variant of melanoma that comprises approximately 1% of all cases.[45] Histologically, it is characterized by pleomorphic dermal spindle cells with a marked fibrogenic (stromal) component and may exhibit perineural invasion, intraneural invasion and neural transformation. Clinically, DM presents as a subtle plaque, nodule or dermal thickening which is often (46-93%) amelanotic[46] in chronically sun exposed areas and may be occasionally associated with adjacent lentigo maligna. It is more common in older patients (median age 61 years).[45] Given the nondescript histological and clinical findings, DM is often initially misdiagnosed. As such, patients often present late with locally advanced, thicker lesions (mean Breslow depth 6.5 mm) with malignant cells extending deeply into the reticular dermis and subcutaneous tissue.[47]

The biology and clinical behavior of DM resembles that of a soft tissue sarcoma with high local recurrence rate and a low incidence (4%) of regional lymphatic spread, despite deep invasion.[48] The higher incidence (20%) of distant metastasis suggests that DM spreads through hematogenous rather than lymphatic routes.[46] Moreover, unlike other histological subtypes of melanoma, risk of recurrence and prognosis of DM is not influenced by the regional nodal status.[48] Therefore, many authors do not recommend lymphatic mapping or SLNB and limit lymphadenectomy to those with clinically palpable disease. While DM is a locally aggressive variant of melanoma, it has a better overall survival than other melanoma subtypes with a 5-year overall survival of 75%.[49] Surveillance strategies should reflect the high incidence of local recurrence and the propensity for pulmonary metastasis.[47]

DM has a heterogeneous local recurrence rate (7-56%)[46] reflecting the variable incidence of neural invasion and the degree of desmoplasia within the tumor. Neurotropism and pure desmoplasia indicate a propensity for locally aggressive disease and may identify patients who might benefit from local adjuvant therapy. DM's are most commonly (53.2%) located on the head and neck in close proximity to important structures making wide local excision with acceptable cosmesis very difficult to achieve.[46] Studies show that a minimum of a 1 cm margin is needed to reduce local recurrences and improve overall survival.[45,48-50] However, the majority of DM are deep and the National Comprehensive Cancer Network (NCCN) guidelines recommend at least a 2 cm margin in tumors deeper than 2 mm. In order to overcome positive or close margins many authors recommend adjuvant radiation; however, given the rarity of this subtype of melanoma the evidence for such practice is based solely on retrospective reviews. One study suggested that adjuvant radiation therapy was well tolerated and reported a local recurrence rate (7.4%) similar to wide excision alone (5.9%) despite having thicker primary tumors and narrow or positive margins in the radiation group.[50] The same study reported no in-transit recurrences in the radiation group compared to five (5%) in the surgery group alone.[50] Another study reported no local recurrences after adjuvant radiation therapy in 15 patients compared to 4 local recurrences in 7 patients without adjuvant radiation.[51] In our practice, we routinely consider the use of adjuvant

radiation therapy for high-risk (presence of neurotropism, depth greater than 4 mm and/or margins less than 1 cm), resected DM.

Subungual Melanoma

Subungual melanoma arises from under the nail bed and is a rare but well recognized form of malignant melanoma. While it was first described in 1834 by Alexis Boyer, much is still unknown about subungual melanomas.[52] The etiology, risk factors, epidemiology, clinical behavior, long-term outcomes, and optimal treatment have not been well characterized.

Prior studies have reported that subungual melanoma comprises anywhere from 0.7% to 3% of all cases of cutaneous melanoma.[53-55] The peak incidence is in the 5th to 7th decades of life.[55-58] While cutaneous melanoma has been found to be more common in Caucasians, subungual melanoma is thought to occur disproportionately more often in dark skinned individuals.[56] While very little has been published on risk factors, some suggest an association with a history of nail trauma in addition to sun exposure.[59]

The most common sites of subungual melanoma are the thumb (34%), great toe (25%), and the middle finger (14%).[57] Clinically, these tumors present with local symptoms (nail color or plate changes, ulceration, mass, bleeding, and pain) or signs of loco-regional or distant metastases. In 1886, Sir Jonathan Hutchinson called it “melanotic whitlow” because it often resembled infection.[60,61] These lesions have been mistaken for hematomas, blisters, and nevi.[56] Hutchinson’s sign is the presence of a longitudinal pigmented streak in the nail fold which has classically been associated with subungual melanoma. To confuse matters, studies have shown that the presence of amelanosis in subungual melanoma may be higher than in other forms of cutaneous melanomas and can represent anywhere from 15-50% of cases.[55,58] As such, a delay in diagnosis has resulted in advanced lesions at presentation.[58,62]

The most common histological subtypes of subungual melanoma are thought to be acral lentiginous and nodular.[55,57,58] Our recent study showed a mean Breslow depth of 3.1 mm at diagnosis and 69% of patients had Clark IV or V histological invasion [57] Optimal diagnosis is made by punch biopsy of the nail bed, but has its limitations because accurate measurement of depth of invasion is often challenging. This is in part due to the poor interface between the papillary and reticular dermis and the paucity of subcutaneous fat in the subungual area, with only dermal collagen separating the nail matrix from the underlying bone. Moreover, epidermal hyperplasia is often seen, which may result in an exaggerated Breslow thickness. The nail matrix also lacks a granular layer, which further complicates this measurement.[53,58] Early recognition of clinical signs and symptoms, together with punch biopsy of the nail bed is essential in suspected lesions.

The prognosis of subungual melanoma is poor and likely related to delay in diagnosis resulting in advanced lesions at presentation. In a case series of 124 cases, recurrence-free survival rates at 5, 10 and 20 years were 57.1%, 49.9%, and 44.4%, respectively.[57] Overall survival rates at 5, 10, and 20 years were 60.5%, 43.8%, and 28.3%, respectively.[57]

Most cases are managed by amputation of the affected digit in order to obtain the recommended clear surgical margins. However, controversy exists in regard to the level of amputation, and only a few limited studies have investigated the optimal surgical treatment secondary to the discrete nature and rarity of these tumors. Historically, surgical therapy has trended towards a more distal level of resection, although it has been shown recently that the level of amputation does not influence survival or outcome in the setting of histologically free margins.[57]

Pediatric Melanoma

Pediatric melanoma (< 18 years old) accounts for 1 – 4% of all melanoma cases and 1 – 3% of all pediatric malignancies.[63] Recent series indicate that there is an increasing incidence of diagnosis among children and young adults.[64,65] The Surveillance, Epidemiology and End Results (SEER) database identified a 2.9% per year increase in the incidence of pediatric melanoma from 1973 to 2001.[65] Reluctance to consider the diagnosis, atypical presentation as pedunculated, amelanocytic and nodular lesions[66] and histological uncertainty with atypical nevi have all been cited as potential causes for the delay in diagnosis.[67,68]

Atypical Spitz nevus exhibit histologic characteristics of both Spitz nevi and melanoma, therefore presenting a diagnostic dilemma for even experienced dermato-pathologists. Terms such as “melanocytic tumors of unknown malignant potential (MELTUMP)” and “spitzoid tumors of uncertain malignant potential (STUMP)” have been used to describe such lesions. Use of SLNB,[69-71] immuno-histochemical stains for Gp100 and Ki67, and molecular analysis for BRAF and NRAS mutations have all been investigated as potential markers. Additionally the use of genomic hybridization and fluorescence in situ hybridization (FISH) may also aid in the distinction of spitz nevi versus melanoma[72,73]; though there exists no single feature or set of criteria that can clearly differentiate an atypical Spitz nevus from melanoma.[74]

Congenital and infantile melanoma are rare with approximately only 23 cases reported in the medical literature.[75] These lesions may develop de-novo in a congenital melanocytic nevus (CMN), or as transplacental metastasis from a primary in the mother.[75,76] Nearly 50% of childhood melanomas arise in association with a pre-existing lesion, most commonly giant CMN[77] and predominantly develop in the dermis, are prone to metastatic dissemination and poor prognosis. It is estimated that these patients carry an approximately 465–fold increased relative risk of developing melanoma, though in only 67% of the patients did the melanoma develop inside the primary nevi.[78]

Other risk factors include: xeroderma pigmentosum, family history, dysplastic nevus syndrome, history of cancer, and hereditary or acquired immunosuppression.[67,79] Role of genetic mutations like *CDKN2A*/ *retinoblastoma (Rb)* gene, *p53* pathways and the *melacortin-1 receptor* pathways remain investigational in children.[80]

Treatment guidelines and strategies for pediatric melanoma are generally extrapolated from adults with surgical management remaining the cornerstone of treatment. Recent pediatric studies have noted a higher rate of sentinel lymph node involvement as compared to adults.[81-84] The role of adjuvant therapy in pediatric patients remains unclear. Three studies

have investigated the safety and feasibility of high dose interferon in children.[83,85,86] Pediatric patients tolerate interferon well, though efficacy remains to be determined. Few pediatric studies have investigated the role of IL-2 for metastatic disease, and in very small numbers.[87,88] Therefore its recommendation for treatment of melanoma in the pediatric population remains investigational and is not FDA approved for this indication. Additionally the two newest agents that were FDA approved for the treatment of metastatic melanoma, vemurafenib and ipilimumab, have not been approved in the pediatric population and should be used with caution.

Minority Populations

Melanoma is a global problem with an increasing incidence nationally. The vast majority of patients afflicted are Caucasians who develop melanoma on sun-exposed skin with most being diagnosed at an early stage and experiencing a favorable outcome. Minority groups are affected by melanoma in varying degrees as depicted in **Table 1**.[89] However, some studies suggest that melanoma arising in minority populations harbors a worse prognosis.[90,91] This has been attributed to a more advanced stage at diagnosis or aggressive histology.[92] Recently, Hu and colleagues found that 18% of Hispanics and 26% of African Americans presented with regional or distant disease, compared to 12% of Caucasian patients.[23] Additionally mean Breslow thickness for Caucasians was 1.62 mm versus 2.59 mm for non-Caucasians; while the acral lentiginous subtype comprised 6/33 (18.1%) of the non-Caucasian patients with melanoma.[93] Socioeconomic factors, language barriers, and health care system factors have also been surmised as contributing to delayed presentation and influencing survival in ethnic minorities.[94,95,96]

Although the current melanoma ethnic profile is dominated by the Caucasian population, by 2050, the non-Caucasian group is projected to be the majority in the United States.[97] Therefore, it is essential to promote clinical awareness and scientific investigation into this unique group.

Familial Melanoma

About 5 to 10% of melanoma patients are members of a familial melanoma cluster.[98] In some affected families, the pattern of melanoma is consistent with an autosomal dominant, highly penetrant, germline mutation.[99] Hallmark features include more than one primary melanoma in the same patient, multiple affected family members in multiple generations on the same side of the family, and relatively younger age at diagnosis.[98] Familial Melanoma Syndrome, Hereditary Dysplastic Nevus Syndrome and Familial Atypical Mole and Malignant Melanoma Syndrome (FAMM) are names used to describe families.

The most well-studied specific gene mutation that causes Familial Melanoma Syndrome is cyclin-dependent kinase inhibitor (CDKN)2A (p16), a cyclin-dependent tumor suppressor gene on the short arm of chromosome nine (9p21).[100] Depending on the family history, up to 40% of patients with a genetic predisposition to melanoma may have a CDKN2A mutation. In addition, CDKN2A mutation carriers appear to have an increased risk for a variety of other cancers; for instance, pancreatic cancer risk is estimated to be 58%[100] by age 80. A separate rare mutation, CDK4, has been detected in only a few melanoma-prone

families. Since the majority of families with an inherited predisposition to melanoma do not have a mutation in either of these two genes, other yet unidentified loci may contribute to some inherited cases.

Although testing for both CDKN2A and CDK4 is commercially available in the United States, its routine use is not considered standard of care.[101] Several concerns complicate genetic testing.[102] Melanoma risk is multifactorial, influenced by factors such as exposure to ultraviolet light,[103] fair skin type, number of nevi and modifier gene mutations in melanocortin-1 receptor (MC1R). Since these factors may affect a family based on environment and shared background,[104] an at-risk member should follow melanoma prevention measures regardless of a negative CDKN2A genetic test. Another cited concern complicating CDKN2A test interpretation is variability in penetrance according to geographic location. For example, a CDKN2A carrier's risk of developing melanoma before age 50 is 13% in Europe, but 32% in Australia.[102] Despite these challenges, large research groups such as the International Melanoma Genetics Consortium have proposed that CDKN2A screening be offered to certain melanoma patients[98] including individuals with three or more primary melanomas, or patients with a primary melanoma and family members affected by two melanomas or two pancreatic cancers.[100] Of clinical note, the recommendations differ according to the population background risk for melanoma. For example, in lower risk populations, patients with two or more primary melanomas meet testing criteria.[98]

As with all mutation testing, patients often benefit from referral to a genetics professional for a detailed discussion of the risks and benefits prior to testing. Tobacco avoidance is recommended for mutation carriers.[100] Studies are underway to more fully assess the overall impact of CDKN2A testing on patient behavior and outcome.[101]

CONCLUSION

In summary, while malignant melanoma is a moderately common malignancy, the incidence rate of which continues to increase in both Caucasian and non-Caucasian populations, there are rare and unusual subtypes that can make diagnosis and treatment challenging. When diagnosed early, surgical resection is often curative. However, once metastatic, the possibility for cure becomes remote. The presented complexities of melanoma diagnosis and therapy necessitate an organized interdisciplinary approach to clinical management emphasizing individualized care. The preceding review is the result of a joint effort of a multidisciplinary team of experts dedicated to the care of patients with malignant melanoma in the setting of a tertiary referral medical center.

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