Melanoma and Cutaneous Malignancies

Mucosal Melanomas: A Case-Based Review of the Literature

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Differentiate mucosal melanoma from cutaneous melanoma and describe its etiology, molecular features, and treatment approaches in surgical, radiation, and medical oncology.
2. Evaluate mucosal melanoma patients with non-metastatic disease for adjuvant radiation to optimize treatment of the primary tumor.
3. Refer appropriate patients for testing for c-KIT mutations and gene aberrations in order to avoid subjecting them to chemotherapy with minimal benefit.

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ABSTRACT

Mucosal melanoma is a rare cancer that is clearly distinct from its cutaneous counterpart in biology, clinical course, and prognosis. Recent studies have shown important differences in the frequencies of various genetic alterations in different subtypes of melanoma. Activating mutations in the *c-KIT* gene are detected in a significant number of patients with mucosal melanoma. This observation has resulted in the initiation of several clinical trials aimed at exploring the role of receptor ty-

rosine kinases that inhibit c-KIT in this patient population. We herein present a comprehensive literature review of mucosal melanoma along with case vignettes of a number of pertinent cases. We further discuss melanomas of the head and neck, the female genital tract, and the anorectum, which are the three most common sites of mucosal melanoma, with a particular focus on the diagnostic, prognostic, and therapeutic data available in the literature. *The Oncologist* 2010;15:772-781

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BACKGROUND

Melanomas stem from malignant transformation of melanocytes, which are derived from the neuroectoderm. Although the majority of melanomas are cutaneous in origin, they occasionally arise from extracutaneous tissues that contain melanocytes, such as uvea, leptomeninges, or the mucosa of the eye, gastrointestinal, respiratory, and genitourinary tracts. We herein present a comprehensive review of mucosal melanoma. Using case vignettes of patients seen in our own practice, we highlight the three most common sites of mucosal melanoma.

EPIDEMIOLOGY AND ETIOPATHOGENESIS

Mucosal melanoma accounts for 1.3%–1.4% of all melanomas; 25%–50% of these cases occur in the head and neck region [1, 2] (Figure 1). The first case of mucosal melanoma in the English literature was reported by Lincoln et al. [3] in 1885. Major differences between mucosal and cutaneous melanoma are listed at a glance in Table 1. Given the fact that melanocytes develop from neuroectoderm, it is not surprising that mucosal melanoma is more common in ectodermally derived mucosal tissues such as the nasopharynx, larynx, tracheobronchial tree, and esophagus, than in non-ectodermally derived tissues. Several epidemiologic and etiologic differences exist between mucosal melanoma and its cutaneous counterpart. Mucosal melanoma presents one decade later on average than melanoma of cutaneous origin [1]. Except for the oral mucosal site, there is no evidence for racial predilection of mucosal melanoma [4–6]. Mucosal melanomas account for 1.3% of melanomas in whites, whereas 11.8% of all melanomas in blacks are mucosal [1]. Because of its hidden location and rich vascularization, mucosal melanoma usually presents at a more advanced stage and is therefore associated with a higher mortality rate than cutaneous melanoma [7]. It seems certain that mucosal melanoma originates from melanocytes present in mucosal tissue [8–11], but exposure to sunlight is not an etiologic factor. Although irritants and carcinogenic compounds in the air, such as tobacco smoke and formaldehyde, have been implicated in the development of head and neck mucosal melanoma, the potential role of these compounds is not clear. Interestingly, hyperproduction of melanocytes in the oral mucosa was shown to be associated with cigarette smoking and resulted in a greater prevalence of pigmented oral lesions [12]. Several authors have reported that about one third of mucosal melanomas in the oral cavity are preceded by oral melanosis [6, 13–17]. Recently, distinct molecular features have been found in mucosal melanomas that differentiate them from their cutaneous counterpart. For instance, whereas activating mutations of the *BRAF* oncogene, in particular the *BRAF*^{V600E} mutation, have been

found in up to 75% of melanomas arising in areas intermittently exposed to the sun [18–20], they are rare in mucosal melanomas [21]. Comparative genomic hybridization has shown distinct patterns of chromosomal aberrations such as gains of 1q, 6p, and 8q in some mucosal melanomas [22]. Recently, gain of function mutations (in particular K642E, L576P, D816H, and V559A), gene amplifications, and overexpression of c-KIT, a receptor tyrosine kinase, were reported in 15 (39%) of 38 mucosal melanomas [23]. Another study reported c-KIT expression in 88% of oral mucosal melanomas, with 22% of the tumors harboring activating mutations [24]. Antonescu et al. [25] found that 15% of anal melanomas had the c-KIT L576P mutation and showed that this mutation was associated with sensitivity to imatinib in vitro. C-KIT is a key regulator of growth, differentiation, migration, and proliferation of melanocytes [26]. It has been shown to recruit and activate a number of intracellular signaling pathways implicated in tumor progression, such as the phosphoinositide 3-kinase/AKT, Src, mitogen-activated protein kinase, Janus kinase, signal transducers and activators of transcription, and phospholipase-C- γ pathways [27]. These data suggest that mucosal melanoma is a separate entity from melanoma and that prognostic and therapeutic information available for cutaneous melanoma is not necessarily applicable to its mucosal counterpart.

DIAGNOSIS

Because of its lack of visibility and absence of symptoms during early stages, the diagnosis of mucosal melanomas is often delayed. Furthermore, it can be challenging to differentiate a primary mucosal melanoma from a metastasis of an unknown or regressed cutaneous tumor. The exception to this general principle is conjunctival melanoma. Even though conjunctiva is a clear mucous membrane that covers the sclera and lines the inside of the eyelids [28], melanoma arising from this tissue differs from other mucosal melanomas in several aspects. It is associated with sun exposure [29] and, unlike other mucosal melanomas, conjunctival melanomas commonly arise from an antecedent premalignant lesion. Approximately 50%–75% of cases of conjunctival melanoma arise in a setting of primary acquired melanosis and 20%–25% of patients with conjunctival melanoma have an antecedent benign conjunctival nevus [30–32]. Because of these differences and the differences in treatment and prognosis, conjunctival melanomas should be regarded as a unique entity and are not discussed further in this review.

Most mucosal melanomas are lentiginous (mucosal lentiginous melanoma), followed in incidence by the superficial spreading and nodular types [33, 34]. The malignant cells often form nests or clusters, but can exist as single

Figure 1. Oral melanoma. Also seen in the picture are multiple cutaneous metastatic nodules.

Figure 2. Oral amelanotic melanoma (yellow arrow) seen adjacent to an area of oral melanosis (green arrow).

Figure 3. Vulvar melanoma.

cells. The melanoma cells have large nuclei, often with prominent nucleoli, and show nuclear pseudoinclusions re-

Figure 4. Anorectal melanoma with perianal extension.

sulting from nuclear membrane irregularity [35]. One of the key histologic features of melanoma is the identification of intracellular melanin; however, mucosal melanoma lesions can lack melanin pigmentation (amelanotic melanoma) [36–39] (Figure 2), making the diagnosis even more difficult. Dopa-positive melanocytes can be identified using the dopa reaction to demonstrate tyrosinase activity, but this requires fresh tissue [40]. Therefore, immunohistochemical staining analysis for S-100, HMB-45, Melan-A, microphthalmic transcription factor, tyrosinase, and Mart-1 is critical for making an accurate diagnosis of mucosal melanoma [41]. Other histopathologic features of mucosal melanomas include frequent angioinvasion, multicentricity, and a relative lack of lymphoplasmacytic reaction to the tumor [14].

STAGING OF MUCOSAL MELANOMA

There are no standard guidelines for adequate staging workup in mucosal melanoma. A thorough history and physical examination are extremely important and many experts recommend serum lactate dehydrogenase as well as axial imaging of brain, chest, abdomen, and pelvis and/or positron emission tomography (PET) scans to evaluate the stage and extent of disease at diagnosis. The staging system for mucosal melanoma has also not been well established. Because of the advanced presentation of most cases, Breslow depth alone seems to be of little use in staging of the majority of primary mucosal melanomas. Hence, oncologists use different systems to stage mucosal melanoma. Although some clinicians prefer a simple and practical staging system in which stage I is localized, stage II is regional (lymph node involvement), and stage III is distant disease, most use the American Joint Committee on Cancer (AJCC) staging system, referring to distant metastatic disease as stage IV. Establishment of an effective staging system

Table 1. Comparison of cutaneous and mucosal melanoma

	Cutaneous melanoma	Mucosal melanoma
Tissue of origin	Skin	Mucosal surfaces
Mean age at presentation [1]	55 yrs	67 yrs
Staging	American Joint Committee on Cancer staging applicable	Not established
Presentation	Less than one third present with advanced disease	>50% present with advanced disease
Amelanotic appearance	1.8%–8.1% [109]	20%–25% [13, 110]
Risk factors	Sun exposure	Unknown
Race [1]	White, 94%; black, 0.8%	White, 85%; black, 7%
Role of adjuvant radiation to the primary tumor	Generally no role	Radiation to the tumor bed generally recommended
Activating <i>c-KIT</i> mutations [23–25]	<5%	15%–22%
<i>BRAF</i> ^{V600E} [18–20]	50%–60%	Rare

based on prognostic factors unique to mucosal melanoma would be beneficial.

GENERAL PRINCIPLES OF TREATMENT

There are no randomized trials studying treatment modalities such as surgery, radiotherapy, or chemo-/immunotherapy specifically in mucosal melanoma. Surgical resection remains the treatment of choice and can result in cure [42]. Similar to cutaneous melanoma, surgical resection is warranted for effective local control because of the lack of efficacious systemic treatment options. Although most patients with mucosal melanoma have micrometastases at the time of diagnosis of the primary tumor, adjuvant therapy has not been studied in a randomized fashion because of the rarity of the disease. Most authors recommend adjuvant radiation to the primary sites and lymph node regions. Clinical trials are clearly warranted to evaluate the efficacy of local and systemic adjuvant treatments in decreasing recurrence and improving survival. Although interferon- α 2b is frequently offered to mucosal melanoma patients as systemic adjuvant therapy, it has not been formally studied in this patient population. With emerging data on *c-KIT* mutations/overexpression in mucosal melanoma and the efficacy of *c-KIT* tyrosine kinase inhibitors in treating metastatic mucosal melanomas, it would be interesting to study the role of these agents in the adjuvant setting.

Treatment modalities used for advanced cutaneous melanoma, such as dacarbazine, temozolomide, the Dartmouth regimen (dacarbazine, cisplatin, carmustine, and tamoxifen), biochemotherapy, and high-dose interleukin-2, have not been systematically studied in mucosal melanoma. Consequently, patients with metastatic disease from a mucosal primary are commonly treated with standard regi-

mens for cutaneous melanoma, extrapolating from the literature largely derived from patients with cutaneous melanoma. The response rate for single-agent treatment with dacarbazine in advanced cutaneous melanoma was reported to be around 20% in a 30-year overview [43], whereas more recent, large trials suggest it to be lower than that (7%–14%) [44–46]. Combination chemotherapy or biochemotherapy results in higher response rates, in the range of 35%–45%, but is associated with significant toxicity and has not been proven to increase overall survival [47, 48]. Given these disappointing outcomes and lack of effective treatment regimens, entry into a clinical trial is considered an acceptable standard of care for patients with newly diagnosed stage IV melanoma and is in fact the preferred choice in most centers. Novel agents for the treatment of advanced melanoma are being extensively investigated and patients with mucosal melanoma are eligible for most clinical trials in melanoma. Perhaps more intriguing is the fact that, in recent years, different molecular subtypes have been defined in melanoma and this knowledge is being translated into clinical trials, providing the opportunity to rationally treat patients with mucosal melanoma based on molecular characteristics. A study by Curtin et al. [23] in 2006 shed light on *c-KIT* genetic alterations in melanoma. That study showed that *c-KIT* amplification/mutation occurred in 39% of mucosal melanomas, but none of non-chronic sun damage cutaneous melanoma cases. Mucosal melanoma has been shown to exhibit amplifications or increased copy numbers of the 4q12 locus by comparative genomic hybridization. Mutations, including the activating K462E mutations of the *c-KIT* kinase domain, which are known to render sensitivity to imatinib (a tyrosine kinase inhibitor) in gastrointestinal stromal tumors, are also commonly seen

in mucosal melanoma. The prevalence of these mutations in mucosal melanoma is 5%–22% based on some studies [23, 25, 49], which is much lower than what was originally expected. Preclinical studies have shown sensitivity of *c-KIT* mutant mucosal melanoma, providing a rationale for studying imatinib in this melanoma type in clinical trials. Marked tumor regression was reported in a patient with metastatic mucosal melanoma who was treated with single-agent imatinib [50]. This observation has been substantiated by several other anecdotal reports, demonstrating objective responses in patients with advanced mucosal and acral melanoma after imatinib monotherapy [51, 52]. A phase II trial investigating response to imatinib in patients with unresectable melanoma harboring somatic alterations of *c-KIT* is currently ongoing at six institutions, including Memorial Sloan-Kettering Cancer Center and our institution.

FOLLOW-UP

Similar to high-risk cutaneous melanoma, close follow-up with thorough physical examinations and appropriate imaging studies for symptomatic patients is necessary for patients with mucosal melanoma after surgical resection. Follow-up for at least 5 years is recommended because recurrence can occur many years after the original diagnosis.

PROGNOSIS AND OUTCOME

Primary melanoma arising in the mucous membranes is an aggressive disease. The best likelihood for favorable outcome is early detection and excision, but as stated earlier, many patients present with advanced disease at diagnosis. Even for patients with presumed early-stage disease, the outcome is generally poor [1, 14], possibly because of occult metastases at presentation. Local treatment failure is a significant problem for most treated patients and distant metastases are also very common. Local recurrence is usually a harbinger for concurrent or subsequent distant metastases [53–55]. There are very few data available regarding the prognosis of patients with metastatic mucosal melanoma because most studies coalesce all metastatic cases regardless of the site of the primary. Distant spread in general is associated with rapid clinical deterioration and a short survival time [56, 57].

MUCOSAL MELANOMAS OF THE HEAD AND NECK

Case Vignette 1

A 52-year-old black man presented with complaints of persistent nasal congestion for several months. He had also been noticing blood streaks in his mucus for several weeks before he was seen by his internist. He was referred to an otorhinolaryngologist after a course of antibiotics failed to clear his symptoms. Endoscopic examination revealed a large grayish-black ulcerated mass within the left maxillary

sinus. A biopsy was obtained and showed melanoma. The patient underwent a medial maxillectomy; the final pathology confirmed the diagnosis of sinonasal melanoma, measuring 3.5 cm in greatest dimension. Lymphovascular invasion and involvement of the sinonasal bone were noted. The patient then underwent a course of radiation therapy to the tumor bed and was subsequently enrolled in an adjuvant vaccine trial using autologous CD4⁺ T-cell clones specific for the cancer-testis antigen NY-ESO-1. The patient was recurrence free for 6 months, at which point he developed metastases to the liver and the small bowel. He was treated with carboplatin, paclitaxel, and sorafenib in the Eastern Cooperative Oncology Group 2603 trial, which resulted in disease control for 6 months, after which disease progression was noted in the liver on imaging studies. Second- and third-line treatment with dacarbazine and IMC 1121B (an antibody directed against vascular endothelial growth factor receptor 2), respectively, in a phase II trial failed to control further progression of disease.

Mucosal melanomas of the head and neck (MMHN) account for 6%–20% of all malignant melanomas of the head and neck region and for about 1% of all melanomas [14, 58]. The most common sites for MMHN are the sinonasal (55%) and oral (40%) cavities [14, 54, 58–60]. Other rare sites include the pharynx, larynx, and esophagus [17, 61, 62]. The exact origin of sinonasal lesions is often difficult to identify, mainly because these tumors can transgress multiple subsites and are often locally advanced at presentation. Approximately 80% of sinonasal melanomas are believed to occur in the nasal cavity, whereas about 20% originate in the sinuses. Within the nasal cavity, the lateral wall and the conchae are most frequently involved. Among the paranasal sinuses, the maxillary sinus is the most common site, followed by the ethmoid, frontal, and sphenoid sinuses. In the oral cavity, the hard palate and maxillary alveolus are the predominant sites of involvement [14, 54].

MMHN has a peak incidence in patients aged 60–80 years, and some studies have noted a slight male preponderance. The incidence of MMHN appears to vary by race and ethnicity. Mucosal melanoma, particularly in the oral cavity, is relatively common in Japan. In one series, oral melanoma made up 7.5% of all melanomas and 35% of mucosal melanomas [6], much higher than what has been reported in white (<1% and 3.6%, respectively) [1]. Another study reported an incidence of 10% for all melanomas in the oral or nasal cavities and of mucosal origin in Ugandans [5].

The most frequent symptoms in patients with sinonasal melanomas are epistaxis, nasal obstruction, diplopia, and proptosis [34]. Patients with oral cavity melanoma may present with friable, pigmented masses, ill-fitting dentures, ulceration, or bleeding, but many of these lesions are dis-

covered incidentally during routine oral or dental examinations [14, 15]. The vast majority of patients with MMHN do not have early symptoms, and many studies have noted a lag time from the appearance of symptoms to evaluation by a health care professional from several weeks to as long as 2 years [14–17, 63]. In addition, approximately one third of oral melanomas are amelanotic, contributing to late diagnosis in some cases [58, 60, 64]. Approximately 20% of MMHN patients present with lymph node metastases and 10% present with distant metastases [14]. The incidence of nodal metastases is considerably higher in patients with oral cavity melanoma than in patients with sinonasal melanoma [54].

The national cancer database report by Chang et al. [1] noted 2-year and 5-year survival rates for MMHN of 54% and 32%, respectively. In one pooled analysis from five different case series, patients with nasal mucosal melanoma had a 31% 5-year survival rate, whereas sinus melanoma patients had a 0% 5-year survival rate [14]. For patients with oral cavity melanoma, the 5-year survival rate was 12.3% and for pharyngeal melanoma it was 13.3% [14]. In a retrospective study of 59 patients with MMHN, advanced clinical stage at presentation, tumor thickness >5 mm, the presence of vascular invasion, and the development of distant metastases were significant prognostic factors for disease-specific survival [54]. Harwood et al. [65] noted that nodal metastases at presentation and vascular invasion predict a higher risk for local failure and poor disease-specific survival.

Surgical resection is the primary treatment for localized melanomas irrespective of involvement of the regional lymph nodes. Unfortunately, complete resection achieving melanoma-free margins is often difficult in MMHN because of the close proximity of critical anatomic structures; this likely contributes to the high local recurrence rate, which has been reported to be 50%–90% [14, 55, 66–71]. Local recurrences are also presumably related to the presence of satellite formation, multifocality, angiolymphatic invasion, and submucosal spread, which are common features in oral cavity melanoma. In view of this locally aggressive growth pattern, even seemingly early, localized lesions may require radical surgery with planned reconstruction for optimal tumor control [54, 60]. The literature on prophylactic lymph node dissection for MMHN is sparse, but the procedure is not advocated as a treatment for MMHN by most authors [14, 60, 69, 72, 73]. Sentinel lymph node biopsy (SLNB) for patients with MMHN is still under investigation [74]. Adjuvant radiotherapy was shown to improve local control in some recent studies but has not been demonstrated to significantly improve survival in retrospective analyses [75]. Based on retrospective analyses, Stern and Guillaumondegui [55] initially recommended adjuvant radiation therapy for patients with gross residual dis-

ease following surgical excision; however, many authors now recommend postoperative radiotherapy for almost all cases because of the high risk for local recurrence even after complete resection of apparently localized tumors [76, 77]. Despite aggressive treatment measures, >50% of patients experience local treatment failure, and salvage treatment is effective in only 25% of these cases. In addition, several authors have observed that, in many patients, local failure is a harbinger of distant metastases. A meta-analysis showed that 73.1% of patients who had local failure developed distant metastases, whereas those with local control developed distant metastases at a rate of 52.1% [14]. Stern and Guillaumondegui [55] reported that 24 (88.8%) of their 27 patients with MMHN who died from distant metastases had also failed locally or elsewhere in the neck. Mainly because of the low incidence of MMHN, no trials that systematically explore adjuvant chemo/immunotherapy in this disease have been conducted to date.

MALIGNANT MELANOMAS OF THE FEMALE GENITAL TRACT

Case Vignette 2

A 77-year-old woman with a past medical history significant for orbital lymphoma several years prior, who had been treated with chemotherapy and radiation, presented to her primary gynecologist complaining of dysuria. Physical examination revealed a 3-cm pigmented lesion in the vulva; a core biopsy was performed and showed melanoma. The patient underwent a partial vulvectomy with SLNB. The final pathology of the resected tissue showed a malignant melanoma of the vulva measuring 9.5 mm in thickness with no ulceration or vascular invasion. Sentinel lymph node sampling demonstrated microscopic involvement of one left inguinal lymph node. The patient declined a lymph node dissection, and a PET–computed tomography (CT) scan showed no other sites of disease. She subsequently received a 12-month course of GM-CSF (250 μ g s.c., 14 days on, 14 days off) [78], during which she remained recurrence free. However, 1 year after completion of the adjuvant treatment, she developed a left pelvic side wall recurrence that was deemed unresectable. The patient was enrolled in a phase II trial using imatinib in patients with inoperable melanoma harboring somatic alterations of *c-KIT*. The melanoma tested positive for the L576P *c-KIT* mutation and the patient was started on 400 mg twice-daily imatinib mesylate, to which she had a complete response that lasted >6 months.

Primary mucosal melanomas of the female genital tract account for 18% of all mucosal melanomas and 3% of melanomas diagnosed in women [1] (Figure 3). The first case of malignant melanoma of the female genital tract (MMFG) was reported by Hewitt in 1861 [79]. The predominant site for MMFG is the vulva, followed by the vagina, whereas

20% of cases are multifocal. Vulvar melanoma is the second most common vulvar malignancy, representing 3.4%–10% of vulvar neoplasms [80–82]. Weinstock reported data on 203 cases of vulvar melanoma, diagnosed in 1973–1987, compiled as part of the Surveillance, Epidemiology, and End Results program [82]. In that study, the incidence of MMFG was 0.108 per 100,000 persons, the 5-year survival rate was 50%, and the average age at presentation was 66 years. A Swedish study of 219 cases of vulvar melanoma diagnosed in 1960–1984 reported an incidence of 0.27 per 100,000 for 1960–1964 and 0.14 per 100,000 for 1980–1984 [81]. The average reported age at diagnosis of vulvar melanoma was in the range of 58–79 in various small series. One case series reported vulvar melanoma in a 10-year old girl [83]. Few risk factors have been identified for this disease. Although cutaneous and vulvar melanomas are likely to be etiologically distinct, observations suggest that a subset of vulvar melanomas share some risk factors with cutaneous melanomas. There is a suggestion that vulvar melanomas develop from contiguous nevi [84]. This may be explained by the fact that mucosa of the female genitalia is contiguous with cutaneous tissue. In fact, most melanomas arising from labia majora are considered cutaneous, whereas those arising from labia minora or clitoria are considered to be of mucosal origin. Other proposed risk factors for vulvar melanoma include chronic inflammatory disease, viral infections, and chemical irritants. A family history of melanoma seems to be a factor in a subset of patients. In a review by Wechter et al. [83], 15% of patients with vulvar melanoma reported a family history of cutaneous melanoma, and one patient was found to have a germline mutation in the melanocortin type I receptor gene.

Symptoms of MMFG that lead to initial presentation are similar to those of other gynecological tumors and include bleeding, abnormal discharge, pruritus, burning pain, dysuria, and the presence of a polypoid mass or ulceration. Most of these lesions are black or gray-black in color and some are amelanotic [85]. The average time from onset of symptoms to first presentation for medical care is approximately 4 months [86]. Multiple staging systems have been proposed for patients with MMFG [87–90]. Because the biologic behavior of vulvar melanoma is similar to that of cutaneous malignant melanomas [91], the AJCC staging system is often used for these tumors. Several reports confirm that lymph node status is the most powerful prognostic indicator for vulvar melanoma, followed by ulceration and tumor thickness of the primary lesion [1, 80–85]. Additional prognostic factors were reported in a number of retrospective series and included age, mitotic rate, amelanosis, emergence within a pre-existing nevus, tumor extension to the lateral labia majora, centralized anatomic location, an-

gioinvasion, DNA nondiploidy, low income, and nonwhite race [1, 81–83, 85]. Although 70% of patients present with clinically localized disease, the overall prognosis is poor. In a Swedish study, the 5-year survival rate was 35%, with rates of 26.8% and 65.2% for node-positive and node-negative vulvar melanomas, respectively [81].

Treatment for primary localized vulvar melanoma is surgical excision with adequate tumor-free margins. Multiple studies have failed to demonstrate a significant overall or disease-free survival benefit with radical (up to 5-cm margin) versus more conservative (1- to 2-cm margin) surgical resection of vulvar melanoma [80–84, 92–94]. The currently practiced surgical approach consists of a wide excision, with a 1-cm margin of skin for vulvar melanoma with a thickness of <1 mm and a 2-cm margin for thicker lesions [93]. Prophylactic lymph node dissection as a routine procedure is not recommended based on several retrospective studies that failed to show any benefit in clinical outcome [52, 63, 95]. Lymphatic drainage of the vulva is usually first to the superficial inguinal nodes, followed by the cribriform fascia to the deep inguinal or femoral nodes. SLNB is now routinely done in vulvar melanomas that are ≥ 1 mm thick or ulcerated [93, 96–100].

ANORECTAL MELANOMA

Case Vignette 3

An 83-year-old woman presented to a local hospital with rectal bleeding for >1 month. Colonoscopy identified a large, black, friable mass in the rectum, an incisional biopsy of which showed melanoma. She was subsequently referred to our center for further workup and management. A PET–CT scan demonstrated no other sites of disease. The patient underwent a sphincter-sparing resection of the rectal mass followed by adjuvant therapy with low-dose temozolomide for 6 months. Two months after completion of adjuvant treatment, a follow up PET–CT scan documented recurrent disease in the liver and lungs. The patient was not a candidate for a clinical trial because of her poor performance status. After a brief course of single-agent carboplatin, the patient succumbed to her illness.

Anorectal melanoma is rare and accounts for 0.4%–1.6% of all melanoma cases [101] (Figure 4). In one large series, anorectal melanomas represented 0.5% of all colorectal and anal cancers [102]. Similar to melanomas of the female genital tract because of the contiguity of the mucosal and cutaneous tissues, it is important to define the exact anatomic location of anal melanomas because many of them may actually be cutaneous in origin. Like anorectal carcinomas, the diagnosis of anorectal melanoma is often delayed because typical symptoms such as anal pruritus or rectal pain can mimic benign con-

ditions, such as hemorrhoids or rectal polyps. The majority of anal melanoma lesions arise near the dentate line in the anal canal and have polypoid and pigmented features. Anorectal melanoma occurs most often in the fifth to seventh decade of life. Although risk factors are largely unknown, an association with HIV infection has been suggested [103]. Prognostic factors include stage at diagnosis, lymph node status, and tumor thickness [104–108]. Because 20%–65% of patients have distant metastases at presentation, the prognosis is generally poor.

Surgery is the main treatment modality for anorectal melanoma; however, the optimal surgical procedure for primary tumors is controversial. The spectrum of different surgical approaches varies from a relatively simple wide local excision with minimal morbidity to a more extensive resection such as an abdominoperineal resection (APR), which is associated with a very high morbidity rate and functional compromise. However, because of the rarity of anorectal melanoma and the advanced stage at which most patients present, a standard surgical intervention has not been established to date. A retrospective study of 50 patients failed to show an advantage of APR over wide local excision with respect to overall survival, although there was a trend for better local control with APR. Because wide local excision of the primary tumor followed by adjuvant radiotherapy to the pelvis and inguinal lymph nodes may have a similar local control rate as APR [104], many sur-

geons perform local excision (with negative margin) in most patients, reserving APR with or without inguinal lymph node dissection for those with local extensive disease that is not amenable to local excision. Palliative surgery (such as local segmental resection or a diverting colostomy for bowel obstruction) along with systemic therapy is generally advocated for patients with advanced disease (large primary tumors or distant metastases). The presence of metastatic disease has been reported in 20%–62% of patients at the time of initial diagnosis and the prognosis in general for anorectal melanoma is poor, with a 5-year survival rate of about 20% from several studies [101–108].

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