Mucosal Melanoma

Michael A. Henderson, Charles M. Balch, Claus Garbe, Alexander N. Shoushtari, Bin Lian, Chuanliang Cui, and Jun Guo

Contents

M. A. Henderson (✉)
Division of Cancer Surgery, Peter MacCallum Cancer Center, Melbourne, VIC, Australia
e-mail: michael.henderson@petermac.org

C. M. Balch
Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: Balchch@jhmi.edu; cmbalch@mdanderson.org

C. Garbe
Centre for Dermatooncology, Department of Dermatology, Eberhard Karls University, Tuebingen, Germany
e-mail: claus.garbe@med.uni-tuebingen.de

A. N. Shoushtari
Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA
e-mail: shoushta@mskcc.org

B. Lian · C. Cui · J. Guo
Department of Renal Cancer and Melanoma, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University Cancer Hospital and Institute, Beijing, China
e-mail: lianbin0214@126.com; 1008ccl@163.com; guoj307@126.com

C. M. Balch et al. (eds.), *Cutaneous Melanoma*,
https://doi.org/10.1007/978-3-030-05070-2_15

Abstract

Mucosal melanomas are rare tumors which most commonly arise in the upper aerodigestive tract (oral cavity, nasal cavity, and sinuses), anorectum, and female genital tract. Compared to cutaneous melanomas, far less is known about the pathogenesis, natural history, and management of mucosal melanomas. At presentation, mucosal melanomas are characteristically more advanced and associated with poorer outcomes than cutaneous melanomas. The primary treatment modality is complete surgical excision, but due to the anatomical location and advanced stage at presentation, complete removal may not be possible. As the overwhelming majority of patients with locally advanced tumors will die of metastatic disease, highly morbid and/or extensive procedures with major impact on quality of life may not be justified. For patients with advanced disease, immunotherapy with anti PD-1 therapy should be considered and similarly for the small proportion of patients with a c-kit mutation targeted therapy with imatinib may be worthwhile. Unfortunately, the results of treatment for advanced disease do not match those seen for cutaneous melanoma. In this chapter, we review the clinical and pathologic features of mucosal melanomas in general and provide a more detailed discussion concerning the presentation and management of tumors originating in specific anatomical locations. Management of advanced disease is considered separately.

Introduction

Primary melanomas arising from the mucosal epithelium lining the respiratory, alimentary, and genitourinary tracts have been well documented but are relatively rare. Unlike their cutaneous counterparts, for which large databases have been established, most reports of mucosal melanoma outcomes are small, retrospective studies. The rarity of these tumors is partially responsible for the fact that insights into the pathogenesis, natural history, and treatment of mucosal melanomas have not kept pace with the advances made in the understanding and treatment of cutaneous melanoma. Guidelines for the management of mucosal melanoma have been published but given the paucity of high-level data, they are consensus-based recommendations only (Ano-uro-genital Mucosal Melanoma Guideline Development Group; Cancer Council Australia Melanoma Guidelines Working Party). By comparison with cutaneous melanomas, mucosal melanomas lack a clear association with ultraviolet exposure, commonly present at a more advanced stage, behave more aggressively, and overall have a much worse prognosis. There has been considerable debate whether these features are the result of an intrinsic biologic aggressiveness (as even small and thin mucosal melanomas can be fatal), the advanced stage at diagnosis due to the clinically occult location of these tumors, or other factors including lack of a dermal/epidermal junction and the richness of the adjacent vascular and lymphatic supply.

Recent developments in melanoma tumor biology have highlighted differences between cutaneous and mucosal melanomas (see also chapter ▶ "Molecular Pathology and Genomics of Melanoma"). Unlike cutaneous melanomas, BRAF mutations are uncommonly seen in mucosal melanomas whereas c-KIT amplification or mutations which are rarely seen in cutaneous melanomas may occur in up to half of mucosal melanomas (Curtin et al. 2005, 2006). A large Chinese series found a 10% incidence of c-KIT mutations, somewhat lower than reported from North American populations, but a higher rate of BRAF mutations (12%) (Lian et al. 2017b). Not surprisingly, the UV-related mutational burden frequently seen in cutaneous melanomas is not prominent in mucosal melanoma. Rather, increased copy number and structural variations predominate (c-KIT, CCND1, and TERT) (Merkel and Gerami 2017). Variations in the frequency of c-KIT mutations by primary site have been noted; they are uncommon in head and neck melanomas but more common in vulvar melanomas (approximately one-third). Another significant feature that separates mucosal melanoma from cutaneous melanoma is the lack of a validated clinico-pathologic staging system. Unlike the current eighth edition AJCC staging system for cutaneous melanoma which is based on 47,000 patients, the staging systems for sinonasal melanoma and vulvar melanoma are not evidence-based and have not been proven to be as useful (Gershenwald et al. 2017b; Verschraegen et al. 2001; Michel et al. 2014; Chae et al. 2016). In many reports, the standard TNM criteria of cutaneous melanoma staging are employed; however, the lack of a dermal-epidermal junction or a suitable identifiable layer deep to mucosa to define tumor thickness is a major issue. In this chapter, we review the clinical and pathologic features of mucosal melanomas in general and provide a more detailed discussion concerning the presentation and management of tumors originating in specific anatomical locations. Adjuvant therapy and management of the patient with recurrent disease will be considered separately.

Epidemiology

The annual age-adjusted incidence of non-cutaneous melanomas was reported by the Third U.S. National Cancer Survey to be 0.7 per 100,000 persons in 1976 (Scotto et al. 1976). In a large population-based study of over 84,000 cases in the US National Cancer Data Base, melanomas arising from mucosal surfaces accounted for 1.3% of all melanomas along with occult primary melanoma 2.2% and ocular melanoma 5.3%, while 91.2% were cutaneous. The majority of mucosal melanomas arose in head and neck sites (55%), followed by female genital (18%), anorectal (24%), and urinary sites (2.8%) (Chang et al. 1998). The incidence of mucosal melanoma from a longitudinal review of the SEER database (1990–2010) was 2.3 per million persons per year, and unlike cutaneous and ocular melanoma, there was no evidence of any change in the incidence over that period (Bishop and Olszewski 2014). The male to female ratio was 0.4:1 predominantly related to the excess of female genitourinary melanomas. Head and neck mucosal melanoma was seen equally frequently in both sexes. The median age at presentation of mucosal melanoma for all sites is in the seventh decade, considerably older than for cutaneous melanoma (67 years vs. 55 years) (Chang et al. 1998). It is most uncommon to see mucosal melanoma presenting in younger persons.

The incidence of mucosal melanoma is similar for white and Hispanic persons (Chang et al. 1998). Among black persons, the incidence of mucosal melanoma was approximately two-thirds that seen in white persons, however, because of the much lower incidence of cutaneous melanoma in Blacks, the proportion of persons with African-American or Hispanic ethnicity with mucosal melanoma was 8.8% compared to <3% of white persons. Although Japanese people have a much lower incidence of cutaneous melanoma than white persons, mucosal melanomas constitute a higher proportion, with the oral cavity in particular being a relatively common site (Takagi et al. 1974). In a report of nasal cavity mucosal melanoma in Uganda, the incidence was higher in black persons than in white persons (Lewis and

Martin 1967). In a large series (706 patients) from four Chinese centers, the primary anatomic sites were the lower GI tract (26.5%), nasal cavity and paranasal sinuses (23%), gynecological sites (22.5%), oral cavity (15%), urological sites (5%), upper GI tract (5%), and other sites (3.0%). At initial diagnosis, 14.5% were Stage I disease (superficial disease extending to muscularis propria), 41% Stage II (deeply invading tumor beyond the muscularis), 21.5% Stage III (lymph node involvement), and 23.0% Stage IV (Lian et al. 2017b).

Pathological Features and Diagnosis

The presence of melanocytes in the mucous membranes results from migration from the neural crest during embryogenesis. Mucosal melanomas are considered malignant neoplasms originating from local melanocytes, similar to their cutaneous counterparts. Because mucosal melanomas are not uncommonly encountered near mucocutaneous junctions (e.g., anorectal melanomas at the junction of squamous and columnar epithelia of the anal canal), it has been suggested that these melanomas represent extension of tumor from melanocytes in the adjacent skin. The presence of melanoma residing solely within the mucosal epithelium and exhibiting the characteristic junctional activity of primary tumors is well documented, however.

Cutaneous melanomas often metastasize to the gastrointestinal tract, predominantly the small bowel (most commonly the serosal surface), and often in the context of widespread disease but infrequently metastasize to organs with mucosal surfaces. Rarely it may be difficult to differentiate a primary mucosal melanoma from a metastasis from an unknown or regressed cutaneous primary melanoma. The presence of junctional change, a precursor lesion, or preexisting melanosis all suggest a primary mucosal melanoma. A typical UV-associated signature on genomic analysis as seen in many cutaneous melanomas would also argue against a primary mucosal melanoma.

Unlike cutaneous melanoma, a precursor lesion is an uncommon occurrence (<10%). The commonest histological appearance of mucosal melanoma is a broad lentiginous growth pattern in the early radial growth phase characterized by proliferation of atypical melanocytes at the base of the mucosal epithelium. The appearances range from in situ changes through to deeply invasive melanoma (Saida et al. 2004). Mucosal melanomas are often quite thick at diagnosis compared to cutaneous melanoma. This may be due to a combination of late recognition by patients, lack of a dermal junction which may potentially facilitate deeply invasive melanomas developing, or intrinsic aggressive behavior of these lesions with an early vertical growth phase. Classification of mucosal melanoma into standard cutaneous subtypes in many cases is impractical and has been shown to be of limited prognostic significance (Chang et al. 1998).

From a histological standpoint, distinguishing mucosal melanoma from other malignant neoplasms can be a significant diagnostic challenge as mucosal primary lesions not infrequently lack identifiable melanin (e.g., only 65% of oral mucosal melanomas contain pigment). The absence of melanin or obvious features of melanoma may lead to confusion with lymphoma, anaplastic carcinoma, or angiosarcoma, although immunohistochemical analysis (e.g., with S-100, HMB-45) may go some way to resolving this issue.

Staging and Prognosis

The staging criteria for cutaneous melanoma have not been shown to be broadly applicable to mucosal melanoma. Clark levels of invasion as described for the skin are not applicable to mucosal melanoma due to varying anatomic features such as the lack of a dermal-epidermal junction and reticular dermis. Although some studies have attempted to correlate the actual depth of invasion with prognosis and in general patients with thinner lesions have better outcomes, the numbers are small and results have been variable. Similarly, the presence of involved lymph nodes has not been comprehensively shown to be of prognostic significance, presumably due to the high rate of distant metastasis and the extremely poor prognosis of patients with mucosal melanomas. A prospective evaluation of 706 Chinese patients with

mucosal melanoma which excluded penile and vulvar primary lesions failed to find any difference in outcome by site of the primary lesion. Mucosal melanomas arising in the head and neck (nasal, pharyngeal, and oral), gastrointestinal, and gynecological/urological sites had similar outcomes with survival rates at 1 year (88%, 83%, 86%), 2 years (66%, 57%, 61%), and 5 years (27%, 16%, 20%), respectively (Lian et al. 2017b). Factors found to be independently predictive of outcome for patients with Stage I–IV mucosal melanoma included tumor thickness, number of lymph node metastases, and site of distant metastases. Among patients with Stage IV disease, elevated LDH along with tumor thickness, lymph node involvement, and number of sites of distant metastases were associated with outcome (Cui et al. 2018). The predominant sites of distant spread at presentation or subsequently were regional lymph nodes (21.5%), lung (21%), liver (18.5%), and distant nodes (9%). Differences by site of the primary were noted; for instance, compared to other primary mucosal melanomas, oral cavity lesions had a higher incidence of regional nodal metastases (31.7% vs. 19.8%, $p = 0.009$) and a higher incidence of lung metastases (32.5% vs. 18.5%, $p = 0.007$) (Lian et al. 2017).

Mucosal Melanoma of the Head and Neck

The mucosal surfaces of the head and neck are the most common site for mucosal melanomas, accounting for approximately 50% of all mucosal melanomas and 2% of all head and neck melanomas. The oral cavity and nasal cavity including paranasal sinuses account for virtually all head and neck mucosal melanomas (Gavriel et al. 2011). The nasal cavity is the most common site (approximately 40%) along with the paranasal sinuses, which are involved in 10% (Lawaetz et al. 2016). The exact origin of sinonasal mucosal melanoma may be difficult to determine in the case of extensive or advanced tumors. The palate and alveolar ridge, both maxillary and mandibular, are by far the most common sites involved in oral cavity lesions. The remainders are evenly divided among the oropharynx, larynx, and proximal esophagus. Risk factors for the development of head and neck mucosal melanoma have not been identified. Oral melanosis which is a rare condition has been suggested as a precursor lesion; however, confirmatory evidence is lacking (Takagi et al. 1974). Similarly both smoking and exposure to formaldehyde have been implicated but again evidence is lacking.

The time interval from onset of symptoms to diagnosis ranges from weeks to many months, with most studies reporting an interval of 3–6 months (Gavriel et al. 2011). The anatomical site of the tumor and the tumor morphology influence the mode of presentation. Sinonasal lesions are typically polypoid in appearance and at least 50% are pigmented. In many cases, the initial diagnosis is a nasal polyp. Typically, patients complain of epistaxis and/or nasal obstruction and less commonly with diplopia or proptosis, pain, or facial deformity. The maxillary sinus accounts for most sinus mucosal melanoma; the frontal sinus is involved uncommonly and the ethmoid sinus rarely. Lesions located in the oral cavity are characteristically pigmented and flat and present as an ulcer, or with bleeding, discomfort, or ill-fitting dentures. The Japanese experience is different from the pattern described above seen in North America and Europe, with a marked excess of lesions in the oral cavity (Takagi et al. 1974). Despite the fact that head and neck mucosal melanoma has a terrible prognosis, the risk of distant disease at the time of presentation is less than 10%. Regional lymphadenopathy at presentation occurs infrequently (<20%), much more commonly from oral than sinonasal sites (Krengli et al. 2006). The commonest location of lymph node spread is the submandibular lymph node basin(s) and less frequently submental, subdigastric, and supraclavicular areas. Retropharyngeal lymph nodes may be involved in patients with sinonasal melanomas.

Differential Diagnosis

Mucosal melanomas in the oral cavity can be confused with a number of benign lesions (Alawi 2013). Pigmented lesions of the oral cavity

are not uncommon. The most frequently seen are melanocytic macules which are usually small and well circumscribed. Other benign lesions include oral melanoacanthoma, smoker's melanosis, and changes indicating systemic conditions including Cushing's syndrome and adrenal insufficiency. Nevi, although uncommon, can be difficult to distinguish from melanomas and usually biopsy is required to make the definitive diagnosis. Angiomas and other vascular lesions may also mimic mucosal melanomas and again may require biopsy. Patients with Peutz-Jeghers syndrome have typical pigmented lesions on the oral mucosa and lips and in most cases should not represent a diagnostic problem. Finally, the most common source of oral pigmentation is dental amalgam tattooing which can usually be confirmed by the characteristic location of the pigment adjacent to previous dental intervention.

Staging and Prognosis

In older studies, the most commonly used staging system was that proposed by Ballantyne: Stage 1, local tumor only; Stage II, regional lymph node involvement; and Stage III, distant metastasis (Ballantyne 1970). The current staging system is the American Joint Committee on Cancer (AJCC) Cancer Staging Manual for mucosal melanoma of the head and neck published in 2017 (8th edition). This provides a greater level of detail about the extent of the primary tumor and should be used in reporting mucosal melanoma of the head and neck. Regardless of the primary site in the head and neck, survival is poor, ranging from 25% to 45% at 5 years, although most studies report a 5-year survival of approximately 30% (Lopez et al. 2016). Data from the SEER database reported a 5-year survival of 25% (Jethanamest et al. 2011). The 3-year survival from a more recent Danish population database was 45%. The pattern of recurrence in this study of 226 patients was local recurrence in 40%, isolated lymph node recurrence in 3%, distant recurrence alone in 6%, and 23% had recurrence at more than one site (Lawaetz et al. 2016).

Given the limitations of the currently available data, a number of potential prognostic factors have been identified. Patients with sinus melanoma may have poorer outcomes than oral or nasal melanomas possibly due to more advanced disease at diagnosis although this is far from clear (Gavriel et al. 2011; Jethanamest et al. 2011). Although far from unanimous, older individuals and possibly males appear to have worse outcomes. Smaller tumor size and complete resection of the primary tumor were associated with improved survival. As noted above, local recurrence is a common and devastating complication of mucosal melanoma. In general, local and regional recurrence had limited impact on overall survival as these sites of recurrence usually occurred with distant recurrence.

Treatment

The management of head and neck mucosal melanoma is complex, with multiple options and the potential to cause major cosmetic and functional deficits. The current consensus is for patients to undergo complete surgical resection and consideration of postoperative adjuvant radiotherapy if possible. Currently, there is no information on adjuvant systemic therapy for patients with head and neck mucosal melanoma. Pretreatment evaluation should confirm the diagnosis, determine the extent of the primary lesion, and exclude distant spread. Preoperative MRI (or CT) is helpful in assessing operability and operative strategy. Preoperative PET/CT (or CT of head, chest, abdomen, and pelvis) scanning to exclude metastatic disease is recommended, although the risk of spread at presentation is relatively low. Functional endoscopic surgery (FES) is being increasingly used for preoperative evaluation including biopsy and in some cases resection of suitable lesions in the nasal cavity and sinuses. Elective lymphadenectomy is not indicated in view of the low risk of lymph node involvement at the time of presentation, the low rate of subsequent lymph node recurrence, and lack of data supporting improved outcomes. There is a very limited

experience with sentinel node biopsy in head and neck mucosal melanoma. The procedure appears to be technically feasible but the more important question of whether it improves outcomes given the observation that lymph node status has minimal impact on survival has yet to be resolved (Stárek et al. 2006).

There are no prospective reports which directly compare surgery and radiotherapy or the combination of these treatments. A number of older studies described the experience with single modality radiotherapy which tended to report rates of local recurrence inferior to surgical resection although there were reports of complete responses (Lund et al. 1999; Yii et al. 2003). No objective difference in outcome was discernible between primary radiotherapy and surgical resection in these older studies. It had been believed previously (erroneously) that melanoma was resistant to radiation therapy, and hence many of the older studies included patients with extensive and/or inoperable disease. Contemporary reports of radical surgery and postoperative adjuvant radiotherapy report significantly improved rates of local control in the order of 60–70% at 5 years but unfortunately with no significant impact on overall survival (Owens et al. 2003; Temam et al. 2005; Krengli et al. 2006; Moreno et al. 2010). Radiotherapy should be considered for patients with inoperable disease or where the surgical margins are inadequate. An alternative strategy based on developing evidence from the management of regional or distant recurrence of cutaneous melanoma may be to consider the use of CTLA-4/PD-1 blockade either as definitive treatment or in combination with surgery or radiotherapy (see also chapter ▶ "Adjuvant Systemic Therapy for High-Risk Melanoma Patients"). Developments in this area are awaited. The major issue in head and neck mucosal melanoma is the management of distant disease, which has not improved in recent decades. Strategies which target disease progression, introduced at an early stage, would be expected to improve not only overall survival but also local control.

Treatment Overview

Mucosal melanoma of the head and neck is uncommon. While mucosal melanomas of the three most common sites, nasal cavity, oral cavity, and sinuses, are considered together, there are differences in presentation and natural history. At presentation, most patients have no evidence of distant spread. Lymph node involvement at presentation or as an isolated event subsequently is uncommon and prophylactic lymphadenectomy in the definitive primary management of head and neck mucosal melanoma is not indicated. Sentinel node biopsy is technically feasible but whether it improves outcomes is unknown. Patients most likely to benefit are those with early stage and/or small tumors who may be considered for adjuvant immunotherapy if found to have lymph node spread. Where possible complete surgical excision is recommended as definitive treatment, however, the potential for major cosmetic and functional deficits is significant. Overall, adjuvant radiotherapy probably reduces the risk of local recurrence but has no impact on survival. As an alternative to surgery, definitive radiotherapy is inferior in terms of both local control and overall survival and should only be recommended for patients who are unable to undergo surgery or who have gross inoperable disease. The role of adjuvant or neoadjuvant immunotherapy for head and neck mucosal melanoma is yet to be resolved; however, their potential to improve outcomes as seen in cutaneous melanoma suggests that they may be possible strategies in the future. Given the poor prognosis for patients with high-risk melanomas, i.e., larger and thicker lesions, adjuvant or neoadjuvant immunotherapy could be considered regardless of lymph node status.

Female Genital Tract Mucosal Melanomas

Mucosal melanomas involving the female genital tract account for 3% of all melanomas in women. Vulvar melanomas account for the

overwhelming majority of these genital tract melanomas with most of the remainder occurring in the vagina. Melanomas of the cervix and uterus are extraordinarily rare.

Vulvar Melanoma

Mucosal melanomas account for 10% of all malignancies of the vulva. Approximately, one-third of vulvar melanomas arise laterally on the labia majora (31%). A similar proportion is centrally located around the clitoris (31%), and the remainders are located around the vaginal introitus or on the labia minora (Ragnarsson-Olding et al. 1999). Although labeled mucosal melanoma, the skin of the vulva changes from the hair-bearing normal skin of the lateral labia majora through glabrous skin (lacking hair follicles and sweat glands) to typical mucosa of the vaginal introitus. A proportion of vulvar melanomas involve both glabrous skin and mucosa, making distinguishing whether the lesion is primarily a vulvar or a vaginal melanoma difficult. Lesions arising in the hair-bearing skin are frequently pigmented and flat in comparison with more medially located lesions which are elevated and amelanotic in one-third of cases.

The median age at presentation is in the late 60s, and it is very uncommon to see vulvar melanomas in young women. Pigmented lesions of the vulva are not uncommon but usually occur in younger women; biopsy may be necessary if there is any clinical concern. Occasionally, vulvar melanomas present as a chance finding during routine gynecological examination; however, as most patients are elderly, the majority present with discharge, bleeding, or pruritus. Approximately, 70% of patients present with clinically localized disease, although the tumors are often quite extensive, with a median thickness of 4 mm. Twenty percent of patients have inguinal lymph node involvement at presentation and a small proportion present with metastatic disease. Evaluation should include biopsy of the dominant lesion and any surrounding pigmented areas. Appropriate imaging of the pelvis and PET/CT scanning with brain imaging to exclude metastatic disease would appear reasonable. There is currently no location-specific staging system suitable for melanoma of the female genital tract. The commonly used International Federation for Gynecology and Obstetrics (FIGO) staging system for vulvar squamous cell carcinoma is inappropriate for melanoma, and in general, the current AJCC staging system for cutaneous melanoma offers significant advantage and is increasingly used (Moxley et al. 2011; Nagarajan et al. 2017; Seifried et al. 2015). Based on a retrospective review of a relatively large group of 100 patients treated at the MD Anderson Cancer Center, a bivariate T category system encompassing tumor thickness and mitotic rate accurately predicted outcome (Nagarajan et al. 2017).

Prognostic factors associated with poorer outcome include increasing age at presentation, increasing tumor thickness, tumor ulceration, elevated mitotic rate central location (vestibule including the clitoris), vascular invasion, and regional lymph node involvement (Sugiyama et al. 2007; Seifried et al. 2015; Nagarajan et al. 2017). Collected series report 5-year survival rates ranging from 5% to 55% with a mean of 36% (Piura 2008). One large study reported a 5-year survival of 70% for patients with thin lesions (<1 mm in thickness) but less than 20% for patients presenting with regional lymph node involvement (Sugiyama et al. 2007).

The management of vulvar melanoma has evolved from radical bilateral vulvectomy to more nuanced and individualized treatment. In a retrospective review, no difference in outcome was found between radical vulvectomy, simple vulvectomy, or wide local excision. More recent reports indicate similar rates of local control and overall survival following less radical surgery (Phillips et al. 1994; Irvin et al. 2001; Moxley et al. 2011; Tcheung et al. 2012). The appropriate margin of excision is unknown but in a series of 281 patients with lesions <2 mm thick the local recurrence rate was 1.8% and was not effected by margins sizes of 1–2 cm versus 5 cm (Tcheung et al. 2012). Unfortunately, a significant proportion of patients have extensive or central lesions that are not suitable for a limited procedure and may require an anterior exenteration for complete

excision. Radiotherapy is potentially an option in these cases, for unresectable cases, or where the patient refuses surgery. Patients with high-risk features including primary tumors >3 cm in size, close or involved margins, or regional lymph node involvement may benefit from radiotherapy although the morbidity is significant.

The role of elective bilateral lymphadenectomy has been controversial. Prophylactic or elective lymphadenectomy does not improve survival, but the presence of inguinal node spread is a poor prognostic factor (Phillips et al. 1994). The procedure is associated with significant morbidity and should only be undertaken for proven lymph node metastases. Sentinel node biopsy has been reported in the management of vulvar melanoma and appears technically feasible but its role is yet to be defined, given that lymphadenectomy has no impact on outcome (de Hullu et al. 2002; Moxley et al. 2011). If it does have a role, it is likely to be in good prognosis patients with thin melanomas where resection of occult lymph node disease may impact survival.

Vulvar Melanoma Summary

Vulvar melanomas arise from the normal skin of the labia majora through glabrous (non-hair-bearing) skin of the labia minora to the typical mucosa of the vaginal introitus. Melanoma of the vulva is a disease of older women and is uncommon in women under 50 years of age. At presentation, one-fifth of patients will have regional lymph node involvement; however, distant metastatic disease is uncommon (<5%). Over the decades, primary surgical treatment has evolved from radical bilateral vulvectomy and routine inguinal lymphadenectomy to conservative wide local excision. The appropriate margin of excision is not well defined; however, a margin of 1 cm has a low risk of local recurrence. Wider margins do not appear to confer any additional benefit and may potentially be associated with significant morbidity. The extent and location of a small proportion of vulvar melanomas, e.g., central lesions around the clitoris may indicate a need for more radical and morbid procedures, e.g., anterior pelvic exenteration to effect complete excision but at the risk of significant morbidity and reduced quality of life. Radiotherapy has been recommended for patients with inoperable tumors, patients who are unwilling to consider major exenterative procedures, or those considered at high risk of local recurrence, e.g., large tumor size or patients with close or involved margins after wide excision. Radiotherapy certainly reduces the risk of local recurrence but appears to have minimal impact on overall survival and is associated with significant morbidity and reduced quality of life. Although lymph node involvement is associated with poorer outcomes, elective lymphadenectomy has no effect on overall survival, no doubt related to the significant and devastating risk of distant recurrence that is not impacted by the extent of local or regional surgery. Elective lymphadenectomy should not be performed. The role of sentinel node biopsy although technically feasible is currently undefined but may be considered for patients with thin, good prognosis lesions who may benefit from identification and removal of lymph node spread at an early stage. Increasingly as with head and neck mucosal melanoma, based on experience from cutaneous melanoma, adjuvant and neoadjuvant immune and targeted therapies may be expected to have a role in the management of this condition.

Vaginal Melanoma

Vaginal melanoma is a rare malignancy with a fearsome reputation (Piura 2008). The 5-year survival is in the order of no more than 20% (Gadducci et al. 2018). The presentation is similar to vulvar melanoma with discharge, bleeding, and pruritus accounting for the majority of presentations. It is a disease of older women, with a median onset in the late 60s. The appearance is of a nodular lesion which is commonly pigmented. Most vaginal melanomas are located in the lower third on the anterior wall. Given the rarity of this condition, prognostic factors are not well described but thicker tumors (greater than 3 mm in thickness) and lymph node involvement indicate a poor outcome (Tcheung et al. 2012; Vaysse et al. 2013;

Gadducci et al. 2018). The workup should be similar to that used for vulvar melanoma. The surgical approach varies from wide excision with a margin of 1 cm for thinner lesions and 2 cm for thicker lesions. Major resections including vulvectomy, vaginectomy, hysterectomy, and anterior pelvic exenteration may be necessary to obtain clear margins, but the considerable cost in terms of both morbidity and reduced quality of life may not be justified in these very high-risk patients. Alternatively, radiotherapy which may have significant morbidity can be considered. In a series of 38 patients, 35 recurred with a median follow-up of 17 months. Local recurrence alone was seen in 22%, distant only in 63%, and both local and distant in 15%. The median progression-free survival was 11.4 months and median survival 19 months. Postoperative radiotherapy reduced the incidence of local recurrence (1 of 15 vs. 5 of 11patients) but not survival (median survival 29 vs. 16 months, $p = 0.46$) (Frumovitz et al. 2010). Similar to vulvar melanoma, there is no role for elective lymphadenectomy. Sentinel node biopsy has been described for vaginal melanoma and although technically feasible, a role for the procedure has not yet been established.

Vaginal Melanoma Treatment Overview

Vaginal melanoma is less common than vulvar melanoma and is a disease of older women. Overall survival is poor (20% at 5 years). If possible, wide excision with a margin of 1–2 cm is recommended. Major procedures including exenteration or primary radiotherapy have been recommended in the past for extensive lesions; however, the survival outcome for these high-risk patients is very poor. The considerable morbidity and reduction in quality of life associated with major exenterative surgical procedures or radical radiotherapy is considerable and may not be justified given the very poor outcomes. The available evidence does not support the use of elective lymphadenectomy. In the era of immunotherapy and targeted therapies, early introduction of these agents will likely become more common and should be considered.

Cervix and Urethra Melanoma

Melanoma at these two sites is extraordinarily rare and unfortunately presentation is usually at a late stage. As a consequence, 5-year survival is poor (5%) (Piura 2008). For cervical lesions deemed to be operable, total abdominal hysterectomy and pelvic sidewall lymphadenectomy is indicated, otherwise palliative radiotherapy can be considered. Urethral melanomas commonly require an anterior exenteration, alternatively radiotherapy can be considered. Isolated cases of ovarian melanoma have been reported; presentation is usually at an advanced stage, and outcomes are very poor regardless of treatment.

Mucosal Melanoma of the Penis and Scrotum

Melanomas of the penis are very uncommon. Most arise from the glabrous skin of the glans penis and may be difficult to distinguish from urethral melanoma. A significant delay in presentation is common. Regional and/or distant spread is found in one-quarter of patients at presentation (Larsson et al. 1999). Historically, radical penectomy was the recommended procedure; however, conservative procedures are now considered appropriate where feasible. Lymphadenectomy is not recommended and although sentinel node biopsy has been described, its role in overall management is unknown. Prognostic factors indicating poorer outcomes include increasing tumor thickness, tumor ulceration, and size of the primary lesion. Up to 25% of patients will develop a regional recurrence, and overall survival has been reported as 31% at 5 years (van Geel et al. 2007).

Melanomas of the shaft of the penis and scrotum are also very rare and should be managed as for cutaneous melanoma.

Anorectal Mucosal Melanoma

Anorectal melanoma is a rare condition that brings together three closely related primary sites – perianal skin, anal canal, and rectum including the anorectal junction. The surface of

the anorectum varies from stratified squamous epithelium through columnar epithelium and mucosa with reducing numbers of melanocytes with proximal extension. Although anorectal melanomas have traditionally been considered as a group, there is evidence of more than subtle differences in melanomas arising in these sites. For example, the incidence of anorectal melanoma is increasing slightly, predominantly due to an increase in rectal melanoma (Tchelebi et al. 2016). Some differences between the three sites may be expected, e.g., anal canal lesions not infrequently metastasize to inguinal lymph nodes while rectal lesions spread less frequently to regional nodes and typically spread to mesenteric and pelvic nodes.

Approximately 60% of anorectal melanomas arise from the anal canal, 25% from the rectal mucosa, and 15% from perianal skin, although in more recent reports, the proportion of rectal melanomas is increasing (Chen et al. 2016). Anorectal melanoma is a disease of older persons with a median onset in the 60s (Ragnarsson-Olding et al. 2009). There is a slight male preponderance. The commonest presentations are rectal bleeding or a perianal mass which in up to one-third of cases may be confused with a diagnosis of hemorrhoids. Typically, the appearance is of a raised or polypoid lesion, variably pigmented, but in up to 20% particularly in the rectum, the melanoma may be amelanotic. At presentation, one-quarter of patients have evidence of lymph node spread. Distant disease at presentation is also common. Following histologic confirmation of the diagnosis, preoperative workup is directed at excluding regional and distant metastasis (PET/CT or CT scanning including brain). In addition, the extent of the tumor as determined by imaging (MRI or CT scan) and physical examination will indicate whether a wide local excision is appropriate or whether an abdominoperineal resection will be required.

The overall survival for patients with anorectal melanoma is poor, with only one-quarter alive 5 years after diagnosis (Ragnarsson-Olding et al. 2009; Kelly et al. 2011; Hicks et al. 2014; Matsuda et al. 2015). Most recurrences occur within 12 months of diagnosis and factors associated with poorer outcome include tumor size, tumor necrosis, perineural invasion, increasing tumor thickness, positive excision margins, and lymph node involvement. Rectal lesions may have a poorer prognosis but this is far from established. Locoregional recurrence usually occurs in the context of widespread disease. Currently, there is no suitable staging system for anorectal melanoma, but the standard TNM system for cutaneous melanoma is used by many authorities.

Historically, the standard procedure for anorectal melanoma was an abdominoperineal resection. Multiple studies, invariably retrospective, small in size, and collected over many years overwhelmingly report similar survivals for both abdominoperineal resection and sphincter-preserving wide local excision but with a higher rate of local recurrence for patients undergoing sphincter-preserving wide local excision. Sphincter preserving wide excision rather than abdominoperineal resection is now considered the default procedure. At least 60% of patients can be managed by conservative wide local excision. The margin of excision is not well described; however, in a small series a R0 (complete) resection with a minimum 10 mm margin was associated with a reduced risk of local recurrence. There was no difference in survival between an abdominoperineal resection and wide excision if margins were greater than 10 mm (19% at 5 years) (Nilsson and Ragnarsson-Olding 2010). Although lymph node status is an important prognostic factor, elective lymphadenectomy has not been shown to influence survival and generally is not recommended (Perez et al. 2013; Ciarrocchi et al. 2017). Sentinel node biopsy has been described in anorectal melanoma and appears technically feasible. There is controversy, however, over the role of the procedure and whether it improves outcomes, given that most local and regional recurrences are associated with distant recurrence. A small number of studies have combined limited excision with postoperative radiotherapy most notably from the MD Anderson Cancer Center which reported high rates of local and lymph node field control (82% and 88%), with sphincter preservation in 96%. Unfortunately, overall survival was unchanged (30% at 5 years) and long-term radiation associated morbidity was frequent (48%) (Kelly et al. 2011). Transanal approaches to

suitable superficial lesions in the rectum have been described; however, long-term evaluation is lacking.

Anorectal Melanoma Treatment Overview

Anorectal melanoma may arise in the lower rectum, anal canal, or perianal skin. Lymph node involvement at presentation is not uncommon (20%). Long-term survival is poor (25% at 5 years). Prognostic factors indicating a poor outcome include larger tumor size, perineural invasion, increasing tumor thickness, and lymph node involvement. Complete excision with sphincter preservation is recommended rather than abdominoperineal resection. With margins of at least 10 mm, the risk of local recurrence approaches that of abdominoperineal resection. As an alternative to major exenterative surgery or radical radiotherapy, suitable patients may be considered for immune or targeted therapies. Adjuvant radiotherapy may be considered after complete excision for patients with close or involved margins. Local control rates are improved with adjuvant radiotherapy but not overall survival. Elective lymphadenectomy does not improve survival and should not be performed. The role of sentinel node biopsy is undefined; however, in the era of immune and targeted therapies, identification of patients with low-risk primary tumors and lymph node involvement may be an indication for adjuvant therapy. Patients with high-risk features (large tumor size, perineural invasion, increasing tumor thickness, and lymph node involvement) who are at very high risk of death from their melanoma may be considered for adjuvant immune or targeted therapies.

Gastrointestinal Tract Melanoma

A very small number of cases of primary mucosal melanomas arising in the gastrointestinal tract apart from anorectum have been reported, including esophagus, stomach, gall bladder, bile duct, small bowel, and colon. In the esophagus and anorectum, melanocytes are frequently noted and are considered to have migrated from the neural crest. The origin of melanocytes in other sites is less clear. The gastrointestinal tract is a frequent site of metastasis and the possibility that melanomas located in these sites represent metastasis from an unknown primary or regressed primary must be strongly considered. Factors favoring a primary mucosal melanoma include polypoidal appearance, tumor arising in an area of junctional change, and melanocytes in adjacent epithelium.

Occasionally, these tumors are found incidentally during investigation or management of another condition but most patients present with evidence of advanced disease. Surgical resection is indicated; however, in many cases, the extent of the disease precludes a curative procedure. The limited available data would suggest that the outcome for primary gastrointestinal tract melanomas is as bad as that for other mucosal melanomas. Targeted systemic therapy (imatinib) or immunotherapy may be considered.

Mucosal Melanoma Adjuvant Therapy

Early diagnosis combined with appropriate surgical therapy is currently the only potentially curative strategy for mucosal melanoma. Unlike cutaneous melanoma, very few adjuvant studies for mucosal melanoma have been reported. In 2012, a randomized phase II study comparing the activity and safety of observation, high-dose interferon, and chemotherapy (temozolomide plus cisplatin) in 189 resected mucosal melanoma patients was reported (Lian et al. 2013). Patients treated with temozolomide plus cisplatin demonstrated significantly improved relapse-free survival (5.4 vs. 9.4 and 20.8 months, respectively, $P < 0.001$) compared to overall survival (21.2, 40.4, and 48.7 months respectively, $P < 0.01$) than those treated with either high-dose interferon or surgery alone. Based on these results, a multicenter, randomized controlled phase III trial of 204 resected mucosal melanoma patients comparing high-dose interferon with temozolomide plus cisplatin demonstrated a significantly lower risk of relapse and metastasis for patients receiving chemotherapy than high-dose interferon and was not

associated with serious toxicity (Lian et al. 2013). The median relapse-free survival was 15.5 months (95% CI, 11.4–19.7 months) in the chemotherapy group as compared with 9.5 months (95% CI, 8.5–10.5 months) in the interferon group (HR for relapse, 0.56; 95% CI, 0.40–0.77; $P < 0.001$). Estimated median overall survival for the chemotherapy group was 41.2 months and 35.7 months for the interferon group ($P = 0.08$). Currently, an active phase II randomized multicenter study comparing recombinant humanized anti-PD-1 mAb with high-dose interferon-a2b for resected mucosal melanoma (ClinicalTrials.gov number, NCT03178123) has randomized 90 of a planned 220 patients11 (Lian et al. 2017a). At the present time, unlike cutaneous melanoma, data on the role of adjuvant immunotherapy or targeted therapy for mucosal melanoma is lacking. Nevertheless, based on the limited experience with immunotherapy and targeted therapies in patients with advanced mucosal melanoma, it is reasonable to expect some response in the adjuvant or neoadjuvant setting particularly in view of the extremely poor outcomes seen in this disease.

Early diagnosis combined with appropriate surgical therapy is currently the only potentially curative strategy for mucosal melanoma. Unlike cutaneous melanoma, very few adjuvant studies for mucosal melanoma have been reported. In 2012, a randomized phase II study comparing the activity and safety of observation, high-dose interferon, and chemotherapy (temozolomide plus cisplatin) in 189 resected mucosal melanoma patients was reported (Lian et al. 2013). Patients treated with temozolomide plus cisplatin demonstrated significant improvement in relapse-free survival (5.4, 9.4, and 20.8 months, respectively, $P < 0.001$) and overall survival (21.2, 40.4, and 48.7, respectively, $P < 0.01$) than those treated with either high-dose interferon or surgery alone. Based on these results, a multicenter, randomized controlled phase III trial of 204 resected mucosal melanoma patients comparing high-dose interferon with temozolomide plus cisplatin demonstrated a significantly lower risk of relapse and metastasis for patients receiving chemotherapy than high-dose interferon and was not associated with serious toxicity (Lian et al. 2013). The median relapse-free survival was 15.53 months (95% CI, 11.37–19.69 m) in the chemotherapy group, as compared with 9.47 months (95% CI, 8.49–10.45 m) in the interferon group (HR for relapse, 0.56; 95% CI, 0.40–0.77; $P < 0.001$). Estimated median overall survival for the chemotherapy group was 41.20 months and 35.73 months for the interferon group ($P = 0.083$). Currently, an active phase II randomized multicenter study comparing recombinant humanized anti-PD-1 mAb with high-dose interferon-a2b for resected mucosal melanoma (ClinicalTrials.gov number, NCT03178123) has randomized 90 of a planned 220 patients11 (Lian et al. 2017). At the present time, unlike cutaneous melanoma, data on the role of adjuvant immunotherapy or targeted therapy for mucosal melanoma is lacking. Nevertheless, based on the limited experience with immunotherapy and targeted therapies in patients with advanced mucosal melanoma, it is reasonable to expect some response in the adjuvant or neoadjuvant setting, particularly in view of the extremely poor outcomes seen in this disease.

Mucosal Melanoma Systemic Therapy

Until recently, the median survival of patients with advanced mucosal melanoma was only 9 months, considerably shorter than has been reported for melanoma at other sites (Kuk et al. 2016). No difference in survival by the site of the primary mucosal melanoma was noted in this study. Previously, standard chemotherapeutic approaches, predominantly dacarbazine-based as used for cutaneous melanoma, were employed for advanced mucosal melanoma with similar results. A similar median survival of 10 months with an objective response rate of 10% was reported from a historical cohort of patients with mucosal melanoma (Shoushtari et al. 2017). In a phase III study, comparing dactinomycin and fotemustine response rates of 7% and 15%, respectively with median durations of response of 7 and 6 months, respectively were reported (Avril et al. 2004). Standard chemotherapy may still have a role in patients who progress through targeted or immune checkpoint therapies (see also chapter

▶ "Evolving Role of Chemotherapy-Based Treatment of Metastatic Melanoma"). The addition of an anti-VEGF agent, recombinant human endostatin to standard dacarbazine compared to dacarbazine plus placebo was associated with both improved progression-free survival and overall survival (12 months compared to 8 months) (Cui et al. 2013).

The genomic landscape of mucosal melanoma with low rates of BRAF mutations (<5% of cases) but significant rates of c-KIT amplification or mutations in up to 50% has meant that much interest has centered around the role of c-KIT blockade with imatinib (see also chapter ▶ "Molecularly Targeted Therapy for Patients with BRAF Wild-Type Melanoma"). In a small Chinese study of 12 patients with mucosal melanoma and actionable BRAF mutations, 70% had a partial or complete response but the median progression-free survival was only 4.4 months (Bai et al. 2017). Two small studies of 13 and 11 patients respectively with mucosal melanoma and c-KIT mutations or amplification treated with imatinib demonstrated activity in modest proportions with 1 complete response and 1 partial response in one study, and in the other study, the subgroup of patients with mucosal melanoma was not reported (Carvajal et al. 2011; Guo et al. 2011). In a subsequent phase II trial in 24 patients with c-KIT mutated or amplified mucosal melanoma, 7 patients had a partial response and 5 stable disease with a median duration of response from 3 to 11 months (Hodi et al. 2013). Responses were only seen in patients with c-KIT mutations, most often in exon 11 (e.g., L576P).

Immune checkpoint inhibition with ipilimumab, a CTL A4 inhibitor, has been reported in a small number of cases mostly pretreated with standard chemotherapy. In summary, the response rates were low, e.g., 6.7% (Postow et al. 2013; Zimmer et al. 2015) (see also chapter ▶ "Systemic Therapy for Mucosal, Acral, and Uveal Melanoma"). In a study of 71 patients from an Italian ipilimumab expanded access program, the overall response rate was 12% (Ascierto et al. 2014). PD-1 inhibitors either as single agent nivolumab or pembrolizumab or in combination with ipilimumab have demonstrated modest activity. A pooled analysis of 88 patients who received either single agent nivolumab or combination nivolumab and ipilimumab reported response rates of 23% and 37% and median progression-free survival of 3 and 6 months, respectively (D'Angelo et al. 2017). Although the response rate for mucosal melanoma was significantly less than for cutaneous melanoma (37% and 60%, respectively) and median progression-free survival was poorer (3 and 12 months, respectively), toxicity was similar but responses appeared to be durable (D'Angelo et al. 2017). In an attempt to improve immune checkpoint blockade, a phase 1b study of anti-PD-1 (JS001, a humanized IgG4 monoclonal antibody) combined with axinitib, a multikinase inhibitor of angiogenesis via VEGF, PDGFR, and KIT, reported an objective response rate of 61% with ongoing partial responses or stable disease in 20 of 33 patients (Guo et al. 2018).

In summary, responses to targeted therapy predominantly with imatinib are well described, but response duration is usually short. The response rate to immunotherapy, in particular anti-PD-1 monotherapy, appears to be lower than is seen in cutaneous melanoma. Attempts to improve outcomes are ongoing, and patients with advanced mucosal melanoma should be strongly considered for clinical studies.

References

Alawi F (2013) Pigmented lesions of the oral cavity: an update. Dent Clin N Am 57:699–710

Ano-uro-genital Mucosal Melanoma Guideline Development Group Melanoma Focus Ano-uro-genital Mucosal Melanoma Guidelines. https://melanomafocus.com/activities/mucosal-guidelines. Accessed 23 July 2018

Ascierto PA, Simeone E, Sileni VC et al (2014) Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort. J Transl Med 12:116

Avril MF, Aamdal S, Grob JJ et al (2004) Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol 22:1118–1125

Bai X, Mao LL, Chi ZH et al (2017) BRAF inhibitors: efficacious and tolerable in BRAF-mutant acral and mucosal melanoma. Neoplasma 64:626–632

Ballantyne AJ (1970) Malignant melanoma of the skin of the head and neck. An analysis of 405 cases. Am J Surg 120:425–431

Bishop KD, Olszewski AJ (2014) Epidemiology and survival outcomes of ocular and mucosal melanomas: a population-based analysis. Int J Cancer 134:2961–2971

Cancer Council Australia Melanoma Guidelines Working Party Clinical practice guidelines for the diagnosis and management of melanoma. https://wiki.cancer.org.au/australia/Guidelines:Melanoma. Accessed 8 Feb 2018

Carvajal RD, Antonescu CR, Wolchok JD et al (2011) KIT as a therapeutic target in metastatic melanoma. JAMA 305:2327–2334

Chae WY, Lee JL, Cho D-H et al (2016) Preliminary suggestion about staging of anorectal malignant melanoma may be used to predict prognosis. Cancer Res Treat 48:240–249

Chang AE, Karnell LH, Menck HR (1998) 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 83:1664–1678

Chen H, Cai Y, Liu Y et al (2016) Incidence, surgical treatment, and prognosis of anorectal melanoma from 1973 to 2011: a population-based SEER analysis. Medicine (Baltimore) 95:e2770

Ciarrocchi A, Pietroletti R, Carlei F, Amicucci G (2017) Extensive surgery and lymphadenectomy do not improve survival in primary melanoma of the anorectum: results from analysis of a large database (SEER). Color Dis 19:158–164

Cui C, Mao L, Chi Z et al (2013) A phase II, randomized, double-blind, placebo-controlled multicenter trial of Endostar in patients with metastatic melanoma. Mol Ther 21:1456–1463

Cui C, Lian B, Zhou L et al (2018) Multifactorial analysis of prognostic factors and survival rates among 706 mucosal melanoma patients. Ann Surg Oncol 25(8): 2184–2192

Curtin JA, Fridlyand J, Kageshita T et al (2005) Distinct sets of genetic alterations in melanoma. N Engl J Med 353:2135–2147

Curtin JA, Busam K, Pinkel D, Bastian BC (2006) Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 24:4340–4346

D'Angelo SP, Larkin J, Sosman JA et al (2017) Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol 35:226–235

de Hullu JA, Hollema H, Hoekstra HJ et al (2002) Vulvar melanoma: is there a role for sentinel lymph node biopsy? Cancer 94:486–491

Frumovitz M, Etchepareborda M, Sun CC et al (2010) Primary malignant melanoma of the vagina. Obstet Gynecol 116:1358–1365

Gadducci A, Carinelli S, Guerrieri ME, Aletti GD (2018) Melanoma of the lower genital tract: prognostic factors and treatment modalities. Gynecol Oncol 150:180–189

Gavriel H, McArthur G, Sizeland A, Henderson M (2011) Review: mucosal melanoma of the head and neck. Melanoma Res 21:257–266

Gershenwald JE, Scolyer RA, Hess KR et al (2017a) Melanoma of the skin. In: Amin M, Edge SB, Greene FL et al (eds) AJCC cancer staging manual, 8th edn. Springer, Switzerland, pp 563–585

Gershenwald JE, Scolyer RA, Hess KR et al (2017b) Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 67(6):472–492

Guo J, Si L, Kong Y et al (2011) Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol 29:2904–2909

Guo J, Sheng X, Si L, et al (2018) A phase Ib study of JS001, a humanized IgG4 mAb against programmed death-1 (PD-1) combination with axitinib in patients with metastatic mucosal melanoma. J Clin Oncol (suppl–abstr 9528)

Hicks CW, Pappou EP, Magruder JT et al (2014) Clinicopathologic presentation and natural history of anorectal melanoma: a case series of 18 patients. JAMA Surg 149:608–611

Hodi FS, Corless CL, Giobbie-Hurder A et al (2013) Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol 31:3182–3190

Irvin WPJ, Legallo RL, Stoler MH et al (2001) Vulvar melanoma: a retrospective analysis and literature review. Gynecol Oncol 83:457–465

Jethanamest D, Vila PM, Sikora AG, Morris LGT (2011) Predictors of survival in mucosal melanoma of the head and neck. Ann Surg Oncol 18:2748–2756

Kelly P, Zagars GK, Cormier JN et al (2011) Sphincter-sparing local excision and hypofractionated radiation therapy for anorectal melanoma: a 20-year experience. Cancer 117:4747–4755

Krengli M, Masini L, Kaanders JHAM et al (2006) Radiotherapy in the treatment of mucosal melanoma of the upper aerodigestive tract: analysis of 74 cases. A Rare Cancer Network study. Int J Radiat Oncol Biol Phys 65:751–759

Kuk D, Shoushtari AN, Barker CA et al (2016) Prognosis of mucosal, uveal, acral, nonacral cutaneous, and unknown primary melanoma from the time of first metastasis. Oncologist 21:848–854

Larsson KB, Shaw HM, Thompson JF et al (1999) Primary mucosal and glans penis melanomas: the Sydney Melanoma Unit experience. Aust N Z J Surg 69:121–126

Lawaetz M, Birch-Johansen F, Friis S et al (2016) Primary mucosal melanoma of the head and neck in Denmark, 1982–2012: demographic and clinical aspects. A retrospective DAHANCA study. Acta Oncol 55:1001–1008

Lewis MG, Martin JA (1967) Malignant melanoma of the nasal cavity in Ugandan Africans. Relationship of ectopic pigmentation. Cancer 20:1699–1705

Lian B, Si L, Cui C et al (2013) Phase II randomized trial comparing high-dose IFN-alpha2b with temozolomide plus cisplatin as systemic adjuvant therapy for resected mucosal melanoma. Clin Cancer Res 19:4488–4498

Lian B, Cui C, Song X, et al (2017a) Phase III randomized, multicenter trial comparing high-dose IFN-a2b with temozolomide plus cisplatin as adjuvant therapy for resected mucosal melanoma. J Clin Oncol (suppl–abstr 9589)

Lian B, Cui CL, Zhou L et al (2017b) The natural history and patterns of metastases from mucosal melanoma: an analysis of 706 prospectively-followed patients. Ann Oncol 28:868–873

Lopez F, Rodrigo JP, Cardesa A et al (2016) Update on primary head and neck mucosal melanoma. Head Neck 38:147–155

Lund VJ, Howard DJ, Harding L, Wei WI (1999) Management options and survival in malignant melanoma of the sino-nasal mucosa. Laryngoscope 109:208–211

Matsuda A, Miyashita M, Matsumoto S et al (2015) Abdominoperineal resection provides better local control but equivalent overall survival to local excision of anorectal malignant melanoma: a systematic review. Ann Surg 261:670–677

Merkel EA, Gerami P (2017) Malignant melanoma of sun-protected sites: a review of clinical, histological, and molecular features. Lab Investig 97:630–635

Michel J, Perret-Court A, Fakhry N et al (2014) Sino-nasal mucosal melanomas: the prognostic value of tumor classifications. Head Neck 36:311–316

Moreno M, Roberts D, Kupferman M et al (2010) Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the MD Anderson Cancer Center. Cancer 116:2215–2223

Moxley KM, Fader AN, Rose PG et al (2011) Malignant melanoma of the vulva: an extension of cutaneous melanoma? Gynecol Oncol 122:612–617

Nagarajan P, Curry JL, Ning J et al (2017) Tumor thickness and mitotic rate robustly predict melanoma-specific survival in patients with primary vulvar melanoma: a retrospective review of 100 cases. Clin Cancer Res 23:2093–2104

Nilsson PJ, Ragnarsson-Olding BK (2010) Importance of clear resection margins in anorectal malignant melanoma. Br J Surg 97:98–103

Owens JM, Roberts DB, Myers JN (2003) The role of postoperative adjuvant radiation therapy in the treatment of mucosal melanomas of the head and neck region. Arch Otolaryngol Head Neck Surg 129:864–868

Perez DR, Trakarnsanga A, Shia J et al (2013) Locoregional lymphadenectomy in the surgical management of anorectal melanoma. Ann Surg Oncol 20:2339–2344

Phillips GL, Bundy BN, Okagaki T et al (1994) Malignant melanoma of the vulva treated by radical hemivulvectomy. A prospective study of the Gynecologic Oncology Group. Cancer 73:2626–2632

Piura B (2008) Management of primary melanoma of the female urogenital tract. Lancet Oncol 9:973–981

Postow MA, Luke JJ, Bluth MJ et al (2013) Ipilimumab for patients with advanced mucosal melanoma. Oncologist 18:726–732

Ragnarsson-Olding BK, Nilsson BR, Kanter-Lewensohn LR et al (1999) Malignant melanoma of the vulva in a nationwide, 25-year study of 219 Swedish females: predictors of survival. Cancer 86:1285–1293

Ragnarsson-Olding BK, Nilsson PJ, Olding LB, Nilsson BR (2009) Primary ano-rectal malignant melanomas within a population-based national patient series in Sweden during 40 years. Acta Oncol 48:125–131

Saida T, Kawachi S, Takata M et al (2004) Histopathological characteristics of malignant melanoma affecting mucous membranes: a unifying concept of histogenesis. Pathology 36:404–413

Scotto J, Fraumeni JFJ, Lee JA (1976) Melanomas of the eye and other noncutaneous sites: epidemiologic aspects. JNCI 56:489–491

Seifried S, Haydu LE, Quinn MJ et al (2015) Melanoma of the vulva and vagina: principles of staging and their relevance to management based on a clinico-pathologic analysis of 85 cases. Ann Surg Oncol 22: 1959–1956

Shoushtari AN, Bluth MJ, Goldman DA et al (2017) Clinical features and response to systemic therapy in a historical cohort of advanced or unresectable mucosal melanoma. Melanoma Res 27:57–64

Stárek I, Koranda P, Benes P (2006) Sentinel lymph node biopsy: a new perspective in head and neck mucosal melanoma? Melanoma Res 16:423–427

Sugiyama VE, Chan JK, Shin JY et al (2007) Vulvar melanoma: a multivariable analysis of 644 patients. Obstet Gynecol 110:296–301

Takagi M, Ishikawa G, Mori W (1974) Primary malignant melanoma of the oral cavity in Japan. With special reference to mucosal melanosis. Cancer 34:358–370

Tchelebi L, Guirguis A, Ashamalla H (2016) Rectal melanoma: epidemiology, prognosis, and role of adjuvant radiation therapy. J Cancer Res Clin Oncol 142: 2569–2575

Tcheung WJ, Selim MA, Herndon JE 2nd et al (2012) Clinicopathologic study of 85 cases of melanoma of the female genitalia. J Am Dermatol 67:598–605

Temam S, Mamelle G, Marandas P et al (2005) Postoperative radiotherapy for primary mucosal melanoma of the head and neck. Cancer 103:313–319

van Geel AN, den Bakker MA, Kirkels W et al (2007) Prognosis of primary mucosal penile melanoma: a series of 19 Dutch patients and 47 patients from the literature. Urology 70:143–147

Vaysse C, Pautier P, Filleron T et al (2013) A large retrospective multicenter study of vaginal melanomas: implications for new management. Melanoma Res 23:138–146

Verschraegen CF, Benjapibal M, Supakarapongkul W et al (2001) Vulvar melanoma at the M. D. Anderson Cancer Center: 25 years later. Int J Gynecol Cancer 11:359–364

Yii NW, Eisen T, Nicolson M et al (2003) Mucosal malignant melanoma of the head and neck: the Marsden experience over half a century. Clin Oncol (R Coll Radiol) 15:199–204

Zimmer L, Eigentler TK, Kiecker F et al (2015) Open-label, multicenter, single-arm phase II DeCOG-study of ipilimumab in pretreated patients with different subtypes of metastatic melanoma. J Transl Med 13:351