Mucosal Melanoma

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Introduction

Malignant melanoma in mucosal membranes is an aggressive and extremely rare disease comprising approximately 0.03% of all cancers and 1.3% of all melanomas (Table 15.1) [1, 2]. In recent years, cutaneous melanoma has been studied in detail, but due to its rarity, mucosal melanoma is poorly described in the literature [2–6]. The present literature often relies on retrospective investigations and the level of evidence is generally low. The epidemiology, etiology, pathogenesis, and prognostic factors remain largely unknown, with no established consensus on appropriate guidelines for either diagnosis or treatment [3–6].

Mucosal melanomas can occur in all mucosal membranes in the body, including the conjunctiva [3]. Apart from conjunctival melanoma, most mucosal melanomas appear in occult locations, and symptoms arise in an advanced stage of disease where lymph node involvement or distant metastases are often present [3–5]. Distant metastasis frequently occurs in the lungs, liver, and bones [3, 5]. The treatment of choice is surgery, but unfortunately long-term survival is still quite difficult to achieve [3, 4]. Furthermore, the clinical diagnosis is often delayed due to the fact that many mucosal melanomas are amelanotic and pathologists seem to be relatively unaware of the diagnosis at these uncommon locations [3, 4]. All of these factors make mucosal melanoma management exceedingly challenging, and novel treatment modalities along with detailed clinical and pathological guidelines are needed in order to improve the prognosis and long-term outcome [2–7]. In this chapter, we describe mucosal melanomas as a specific disease entity with special focus on etiology and management. Although a large part of the vulva is considered modified skin and not true mucosa, vulvar melanoma is also discussed in this chapter.

Epidemiology and Demographics

Conjunctival melanomas along with sinonasal melanomas represent the most frequently occurring mucosal melanomas, each having an incidence of approximately 0.5 per million/year [3, 8–10]. A recent study reported an incidence for sinonasal melanoma of 0.9 per million/year in the Danish population [11]. Anorectal melanomas have an incidence of approximately 0.4 per million/year, while melanoma in the oral cavity and in the vagina has an annual incidence of 0.2 per million/year [3, 7, 9, 12]. Melanoma is the second most common malignant vulvar disease after squamous cell carcinoma, and it appears in approximately 0.2/100,000/year [7]. Smaller series and case studies have reported melanoma

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Table 15.1 Mucosal melanoma of various organ systems

Location	Incidence	Gender ratio (M:F)	Median age (years)	Prognosis (5-year survival)
Conjunctiva	0.5 per million/year	1:1	58	86.3%
Respiratory tract				
Sinonasal	0.5 per million/year	1:1	75	30%
Larynx	60 cases reported	4:1	60	<10%
Lung	30 cases reported	1:1	54	<25%
Gastrointestinal				
Oral cavity	0.2 per million/year	2:1	65	12.5%
Esophagus	337 cases reported	2:1	65	37%
Stomach	20 cases reported	1:1	65	0%
Small intestine	18 cases reported	1:1	56	0%
Colon	12 cases reported	1:1	60	21%
Anorectal	0.4 per million/year	1:2	68	20%
Gall bladder	31 cases reported	1:1	50	n/a
Biliary tract	9 cases reported	8:1	45	0.33%
Urological				
Urinary bladder	18 cases reported	1:1	62	<10%
Urethra	160 cases reported	1:2	73	<10%
Genital tract				
Penis	100 cases reported	Only male	75	22.5%
Vulva[a]	2 per million/year	Only female	68	30%
Vagina	0.2 per million/year	Only female	60	17.4%
Cervix	80 cases reported	Only female	55	7.8%

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[a]The vulva is generally considered modified skin

in numerous other mucosal membranes, but clear incidence rates of these sites are not available [3]. While the incidence of cutaneous melanomas is rapidly increasing, the incidence of mucosal melanomas has been considered stable [3, 5, 13, 14]. However, while the incidence of conjunctival melanoma in the Danish population was found to be stable in the period from 1943 to 1997 [15], recent studies from Finland, Sweden, and Denmark have reported an increasing frequency in these countries [14, 16, 17].

Additionally, the incidence of sinonasal melanoma in the Swedish population has also been found to be increasing in the period from 1960 to 2000 [13]. Furthermore, a recent study has shown the incidence of anorectal melanoma to be increasing in the American population [18]. Overall, slightly more women seem to be affected, with the main reason due to women suffering from anorectal melanoma (M:F = 1:2). This is compounded by the relatively high incidence of melanoma in the female genital tract and vulva [3, 18–24]. Mucosal melanoma is mainly a disease of the elderly, and most patients are diagnosed after their sixth decade of life, regardless of the affected organ system [3–5, 14]. A general racial predisposition does not appear to exist [9, 25, 26]. However, conjunctival melanoma and vulvar melanoma occur almost exclusively in Caucasians, and sinonasal melanoma is also more frequent in Caucasians compared to Blacks [8, 27, 28]. Sinonasal melanoma and especially oral melanoma seem to occur more frequently in Asian populations compared to Caucasians [26]. Oral melanoma has been found to represent up to 8% of all melanomas in Japanese people [2].

Etiology and Pathogenesis

Malignant melanomas are tumors caused by a malignant transformation of melanocytes derived from neural crest cells [3, 5, 29]. Melanocytes

travel along and together with peripheral nerves and other neural crest-derived cells from the neural crest to their definitive destinations in numerous microenvironments, as well as the mucosal membranes [29]. Melanocytes have been found in most mucosal membranes, but their function in these locations remains unknown [30]. Mucosal melanomas share the neural crest origin with melanotic schwannomas and other pigmented neural crest-derived tumors [29]. Melanomas may potentially share more biological features with other neural crest-derived tumors. Mucosal melanomas most frequently arise *de novo* from a single melanocyte located within a mucosal membrane where a preexisting melanotic lesion is not present [8, 30].

Additionally, melanoma may arise in any preexisting melanocytic lesion [30]. Mucosal melanomas have been reported in preexisting benign melanosis (melanotic macule) of the esophagus, nasal cavity, vulva, vagina, and rectum [30–32]. Regarding anorectal and colon melanomas, the clinician must keep in mind that melanosis coli is not a melanocytic lesion. Mucosal melanocytic nevi have been identified in various mucosal membranes, namely in the oral mucosa; however, there is no evidence of increased risk of malignant transformation in these lesions [30, 33]. An exception is conjunctival melanomas that may potentially arise in a conjunctival nevus in 2–40% of the cases [17, 34, 35]. Vulvar melanomas may be divided into those emerging from the follicular skin and those emerging from the glabrous skin (a broad transition zone consisting of modified skin without hair follicles separating true hairy skin on the labia majora and the true mucosal epithelium in the vagina). Interestingly, a Swedish study showed that melanomas of the glabrous skin were almost exclusively *de novo* melanomas, while melanomas of the hairy skin often developed within a preexisting nevus [36].

In the literature, pure mucosal melanoma in situ is a very rarely reported condition [30]. This may be due to authors reporting the lesion under different names, such as atypical lentigo, atypical pigmented macules, precancerous melanoma, and atypical melanotic hyperplasia [30]. Another plausible explanation may be that these lesions never cause symptoms prior to malignant transformation. Due to the lack of symptoms, most are found accidentally by the dentist or a gynecologist during routine clinical examination. Histologically, mucosal melanoma in situ is defined as an intraepithelial proliferation of cytologically atypical melanocytes [37]. These lesions may be found in several organ systems and the prognosis is favorable after complete surgical removal [38]. A German study found a melanoma in situ component in two-thirds of all cases of sinonasal melanomas [37]. Mucosal melanoma in situ needs further investigation and classification in a universal mucosal melanoma staging manual.

In Caucasian populations, 42–75% of conjunctival melanomas seem to arise in a premalignant lesion, a so-called primary acquired melanosis (PAM), which may be considered a melanoma in situ [8, 17, 39]. PAM is mostly considered a clinical diagnosis and is described as a unilateral, flat, brown lesion with patches of pigmentation confined to the conjunctiva with or without involvement of the eyelid skin or cornea [8, 39]. Histopathologically, PAM is characterized by a neoplastic proliferation of the conjunctival melanocytes and by using specific histological criteria. It can be subdivided into PAM with atypia (PAM+) and without atypia (PAM−). PAM+ has a high risk of progression to melanoma, especially when vertical invasion of the epithelium by the conjunctival melanocytes is observed. Pagetoid spread and epithelioid cytology are also features pointing towards progression of a PAM+ lesion to becoming a melanoma [8, 10, 39, 40]. There is much debate in regard to the grading of PAM because the term "melanosis" has been associated with both benign and premalignant lesions. For this reason, a grading system of premalignant lesions using the more appropriate terms "conjunctival melanocytic intraepithelial neoplasia" (C-MIN) and "hypermelanosis" has been proposed [41].

While sun exposure is a known risk factor for the development of a cutaneous melanoma, no clear risk factors have been identified for mucosal melanomas [3, 5]. Exposure to tobacco and formaldehyde has been proposed to play a role in

sinonasal and oral melanoma, but clear evidence is lacking [42, 43]. The presence of *BRAF* mutations along with a UV light signature consisting of multiple cytosine-to-thymine (C > T) transitions in sun-exposed conjunctival melanoma suggests a role of sun exposure in the pathogenesis of these tumors, but further investigations are needed [44].

Molecular Biology and Genetic Features

In recent years, the genetics and molecular features of cutaneous melanoma have been extensively studied with various next-generation sequencing techniques [45]. However, the genomic landscape of mucosal melanomas remains sparsely elucidated. The discovery and application of molecularly based targeted therapies have revolutionized the treatment of melanoma, and this makes the identification of specific molecular targets even more important today and for the future.

Whole-Genome Sequencing

Furney et al. performed whole-genome sequencing and exome sequencing on ten mucosal melanomas from various locations outside of the eye [46]. This study showed that mucosal melanomas carry a relatively low mutational burden. The mucosal melanoma samples harbored an average of 8.193 somatic, single-nucleotide variants (SNVs) [46], while sun-exposed cutaneous melanomas have been found to harbor an average of 84.495 SNVs (i.e., a factor of 10) [47]. The study also revealed a high rate of copy number and structural variants in mucosal melanoma [46, 48]. Other studies have shown that mucosal melanomas have specific patterns of chromosomal aberrations differing from cutaneous melanomas [49, 50]. Overall, these findings suggest mucosal melanomas as a distinct entity driven by distinct molecular pathways [48].

MAPK Pathway: *BRAF*, *NRAS*, and *KIT*

The Ras-Raf-MEK-ERK (or MAPK) pathway is over-activated in most melanomas (Fig. 15.1) [51]. In cutaneous melanoma, activation of this pathway mainly occurs through mutations leading to activation of the *BRAF*, *NRAS*, or *KIT* genes [51]. *BRAF* mutations are found in about 50% of cutaneous melanoma [45]. Similarly, conjunctival melanomas have about the same overall percentage of 50%, resembling the frequency found in cutaneous melanoma [10, 52, 53]. *BRAF* mutations have been identified as early events in conjunctival melanoma development, and these mutations are highly associated with sun exposure [10]. The conjunctiva is the only mucosal membrane exposed to the sun, and most *BRAF* mutated conjunctival melanomas are confined to the sun-exposed bulbar conjunctiva [10]. This suggests that conjunctival melanomas can be induced by both sun exposure and other factors.

Apart from the conjunctiva, *BRAF* mutations only occur in 10–17% of mucosal melanomas [3, 48, 54]. While frequent in cutaneous melanoma, *NRAS* mutations only seem to be present in 5–14% of mucosal melanomas [48, 49, 54]. An exception is a Swedish study that found *NRAS* mutations in 43% of vaginal melanomas, suggesting a different *NRAS* mutation rate among various locations [55].

While both *BRAF* and *NRAS* mutations are rare in mucosal melanoma, the MAPK pathway seems to be frequently activated by mutations in the *KIT* gene. This gene codes for an upstream tyrosine kinase (c-KIT or CD117) ultimately activating the MAPK pathway [48, 51]. Beadling et al. found *KIT* mutations in 15% of mucosal melanomas [56]. Swedish studies have identified *KIT* mutations in 4% (nasal cavity), 9% (anorectal), and 35% (vulva) of mucosal melanomas, suggesting considerable variation between tumor sites [54, 55]. Curtin et al. found *KIT* mutations and copy number increase in 39% of 102 primary mucosal melanomas of various locations [57]. Santi et al. screened 31 anorectal melanomas and

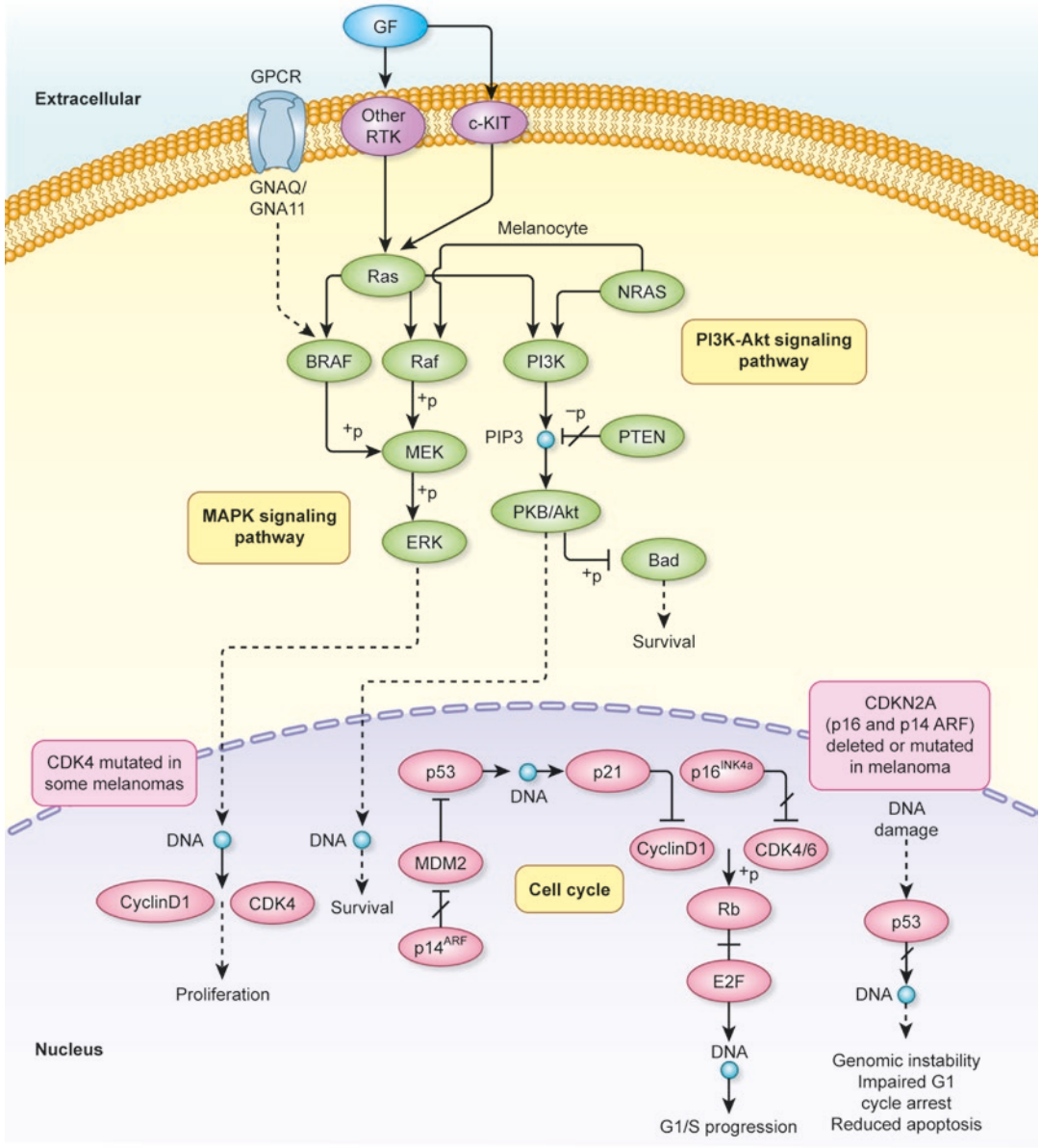

Fig. 15.1 Genetic alterations involved in the development of mucosal melanoma. Mucosal melanoma may develop due to four different mechanisms: activation of the MAPK pathway or the PI3K-Akt pathway, or mutations in the *CDKN2A* or *CDK4* genes. The MAPK pathway may be activated at several levels by mutations in numerous genes, including the *KIT*, *BRAF*, *NRAS,* and *GNAQ/GNA11* genes. Activation of this pathway results in proliferation of the tumor cell. The PI3K-Akt pathway may be activated by mutations in the *NRAS* or the *PTEN* genes resulting in enhanced survival of the tumor cell. Mutations in the *CDK4 or CDKN2A* genes may activate intranuclear pathways allowing the cell to progress into the cell cycle G1/S phase resulting in proliferation. *GF* growth factor, *GPCR* G protein-coupled receptor, *RTK* receptor tyrosine kinase, *P* phosphorylation

found *KIT* mutations in 35.5% [58]. Although there is some variation in the frequency reported by different authors, *KIT* is generally considered more important in mucosal melanoma compared to *NRAS* and *BRAF*.

Other Genetic Features

The PI3K-AKT and CDKN2A pathways have been shown to promote melanomagenesis, and it seems that these pathways are important in the development of mucosal melanoma (Fig. 15.1) [48]. Curtin et al. found a significantly altered expression of *PTEN* (a tumor suppressor that acts as an upstream inhibitor of the PI3K-AKT pathway) in mucosal melanomas compared to other melanoma subtypes [49]. A recent study reported the loss of *PTEN* in 50% of sinonasal melanomas [59]. Total loss of the CDKN2A locus and amplifications of the *CDK4* gene have also been found to be more common in mucosal melanomas compared to other melanoma subtypes [49]. Hsieh et al. found amplification and overexpression of cyclin D1 in 61% of cyclin D1-positive oral melanomas [60]. These findings suggest that the PI3K-AKT and CDKN2A pathways are important in the development of mucosal melanoma, in particular due to the relatively low frequency of identified mutations in genes affecting the MAPK pathway.

Uveal melanomas harbor aberrations of the *GNAQ* or the *GNA11* genes, but these mutations have never been identified in conjunctival melanoma [3]. On the other hand, *NRAS* and *BRAF* mutations are extremely rare in uveal melanoma [3]. *GNAQ/GNA11* mutations are generally not considered to occur in mucosal melanoma, but surprisingly a newer study found *GNAQ/GNA11* mutations in 9.5% (27/284) of mucosal melanomas in Chinese patients [61]. In this study, *GNAQ/GNA11* mutations were associated with a poor prognosis [61]. Targeted treatment for *GNAQ/GNA11* is currently not available [48].

Recent studies have identified *TERT* promoter region mutations in conjunctival melanoma and sinonasal melanomas; however, the role of these aberrations remains unclear [27, 62].

MiRNA Expression

Apart from studies utilizing human melanoma cell lines, the number of studies investigating miRNA in mucosal melanomas is very limited [63]. The largest study identified 25 differentially expressed miRNAs in 37 conjunctival melanomas. In this study, 24 miRNAs were upregulated and 1 was downregulated. Several of the identified miRNAs have previously been found in cutaneous melanoma. The study concluded that there was no difference in the expression of these 25 miRNAs compared to sinonasal melanoma [63]. Additional research is essential in order to identify potential prognostic miRNAs or therapeutic target miRNAs.

Diagnosis

Primary mucosal melanomas are rare conditions, and metastases to the mucosa from other melanomas always have to be excluded [3–5]. Therefore, a detailed clinical history should be obtained focusing on prior cutaneous, ocular, or mucosal melanomas [3]. A clinical full-body examination of the skin with the use of dermoscopy along with a full ophthalmological examination including ophthalmoscopy should always be performed in case of a suspected or confirmed mucosal melanoma [3]. The main differential diagnosis of a pigmented mucosal melanoma is a melanosis or a metastasis from a cutaneous melanoma. Macroscopically, melanomas appear as a flat, macular, or elevated lesion [3, 5]. The tumor may be polypoid, ulcerated, brown to black colored, and/or adherent to underlying tissue [3, 5]. Sinonasal melanomas often present as a polypoid, fleshy, or friable mass [2]. Amelanotic melanomas are frequent in all mucosal locations and may look like most other tumors without any specific tumor characteristics [3]. Most amelanotic vulvar melanomas emerge from glabrous skin [36]. The final diagnosis is made by histopathology [3, 5]. Uveal melanoma with extraocular extension should always be excluded in cases of a conjunctival melanoma [8, 39, 64].

Symptomatology

In general, symptoms of mucosal melanoma present at an advanced tumor stage [3–5]. The symptoms are mostly unspecific and relate to the affected organ system. The hallmark of conjunctival melanomas is the presence of a nodular, elevated tumor of the conjunctiva and only about 60% is pigmented brown or black [8, 14]. Patients with sinonasal melanoma often present with unilateral nasal obstruction, epistaxis, and a mass tumor [65]. In advanced stages, sinonasal melanoma may cause proptosis, diplopia, pain, and facial deformities [9]. Oral melanomas are often asymptomatic [20]. Laryngeal melanomas mainly present with hoarseness due to impingement upon the recurrent laryngeal nerve in some cases [2]. Esophageal melanomas may present with dysphagia and pain, and lower gastrointestinal melanomas may present with bleeding, anemia, bowel obstruction, weight loss, or pain [66, 67]. Urogenital melanomas may present with hematuria, bleeding, discharge, and dysuria [7, 68].

Location

Mucosal melanomas are found in all mucosal membranes, with a tendency for them to appear close to transition zones between the skin and mucosal membranes (Table 15.1) [3]. Studies also show that more melanocytes are found in mucosal membranes closer to the skin (e.g., the oral cavity or rectum) compared to more internal locations, such as the ileum [5]. This may be due to the relatively low number of tight junctions in mucosal membranes compared to the skin, allowing skin melanocytes to travel horizontally from the skin part of the transition zones into the mucosal membrane. Distant metastases from mucosal melanoma are mainly seen in the lung, liver, and non-regional lymph nodes [69]. Most conjunctival melanomas are confined to the sun-exposed limbal zone of the bulbar conjunctiva [8, 14, 34]. Melanomas of the palpebral conjunctiva and caruncle are rare (Fig. 15.2) [8, 14, 34].

Approximately 50% of mucosal melanomas of the head and neck are located in the sinonasal cavity, while about 40% confined to the oral cavity [2–4]. The majority of sinonasal melanomas are located in the anterior part of the inferior turbinates, followed by the septum and the middle turbinates [11, 70]. Melanoma in the paranasal sinuses is rare, with the maxillary sinus being the most commonly affected [11, 70]. Oral melanomas often involve the gingiva and the hard palate, while lesions in the buccal and lip mucosa are very rare [2, 11]. The remaining ~10% of head/neck melanomas are extremely rare and confined to the pharynx, supraglottic larynx, true vocal cords, and lungs [2, 3].

Distal gastrointestinal melanomas represent another large group of mucosal melanomas. The transitional zone is the area surrounding the dentate line that separates the anal skin from the rectal mucosal. It is important to distinguish between melanomas originating from the rectal

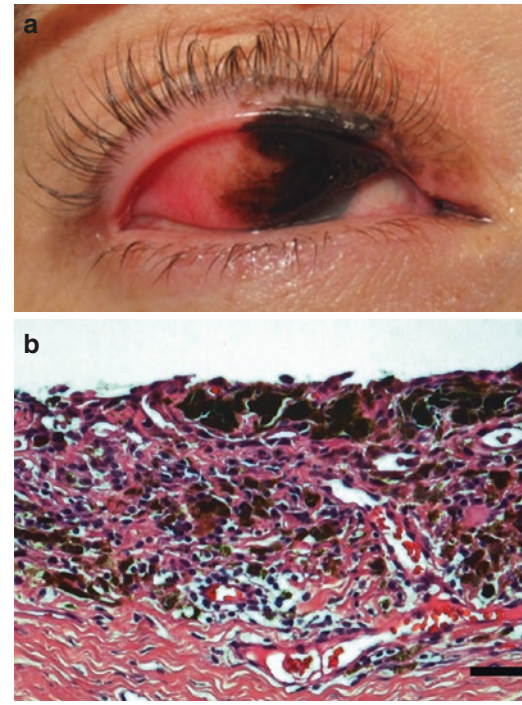

Fig. 15.2 Conjunctival melanoma. (**a**) Clinical photograph showing a conjunctival melanoma involving the upper palpebral conjunctiva. Melanomas at this location are non-UV-exposure induced and may share pathogenic features with mucosal melanomas confined to other sun-shielded mucosal membranes. (**b**) Micrograph of the same conjunctival melanoma. The tumor cells invade the stroma and abundant melanin is present (H&E, bar = 50 μm)

mucosa (about 40%) and those originating from the abundant melanocytes in the proximal anal canal (about one-third), since the latter have a skin origin and are not classified as pure mucosal melanomas [4]. Other gastrointestinal melanomas are mainly found in the middle or lower esophagus, ileum, ascending colon, and neck of the gall bladder. Most vaginal melanomas are located in the anterior wall within the lower third of the vagina [7]. In about 85% of vulvar melanoma, the tumor originates in the labia minora, clitoris, or inner (glabrous, non-hairy) part of the labia majora [7]. Urethral melanoma is often located in the distal part of the urethra [7]. Bladder melanoma can be found in all parts of the bladder [7]. Penile melanoma is often found on the glans [3].

Radiology and Imaging

Radiological examination is important for accurate tumor staging, surgical planning, and surveillance of patients [69, 71]. The Danish Melanoma Group recommends the use of a computed tomography (CT) scan along with magnetic resonance imaging (MRI) in order to characterize the extent of sinonasal melanomas [72]. The National Comprehensive Cancer Network (NCCN) recommends chest imaging in cases of a biopsy-confirmed mucosal melanoma [73]. A positron emission tomography/computer tomography (PET/CT) fusion scan is recommended to detect potential clinically unsuspected metastatic disease [72, 73]. Apart from mucosal melanomas in the head and neck region, CT and PET/CT are of relatively limited value in the evaluation of local disease [71]. The MRI features of mucosal melanoma depend on the melanin content and the presence or absence of hemorrhage [74]. Melanotic melanomas can be separated from other tumors because they reveal a distinct MRI signal pattern comprised of a hyperintense signal on T1-weighted scans and a hypointense signal on T2-weighted scans [74]. Mucosal melanomas are often seen as a homogenous enhancement pattern on MRI [74]. A combined [^{18}F]fluorodeoxyglucose-PET/CT scan has been shown to be superior to a conventional CT scan in detecting lymph node metastasis and distant metastases in anorectal melanoma [24]. Although the role of this scan is well established in cutaneous melanoma management, its utility still needs further validation in large-scale trials regarding mucosal melanoma [71].

Biopsy

Incisional biopsies are associated with an unfavorable prognosis in conjunctival melanoma and should be avoided [14, 40]. There have not been any studies evaluating the role of incisional biopsies in mucosal melanomas outside the conjunctiva, with a standard tissue biopsy, such as a punch or shave biopsy, currently recommended in order to establish the definitive diagnosis [3, 33]. In mucosal melanoma, the diagnosis must be established on the basis of a full-thickness biopsy of the lesion [75]. In vulvar melanoma, excisional biopsies are the preferred method of tissue diagnosis [75].

Histopathology and Immunohistochemistry

Histopathological examination is recommended in all mucosal melanomas in order to confirm the diagnosis and stage of the tumor [3, 72]. The histological features of mucosal melanoma are similar to those found in cutaneous melanomas, with tumors showing a range from epithelioid to spindle-shaped tumor cells, including mixed types (Fig. 15.3). Amelanotic mucosal melanomas are frequently found and have been reported in up to 45% of cases [43]. The melanoma cells may grow in a sheetlike fashion or in nests [3, 8, 37, 39]. Approximately 75% of conjunctival melanomas are associated with a preexisting PAM with atypia, and 20% are associated with a nevus or PAM without atypia [8, 39]. Invasion of tumor cells from the epithelium into the substantia propria is the hallmark of any mucosal melanoma [39].

Pathologic analysis of suspected lesions includes immunohistochemical staining for

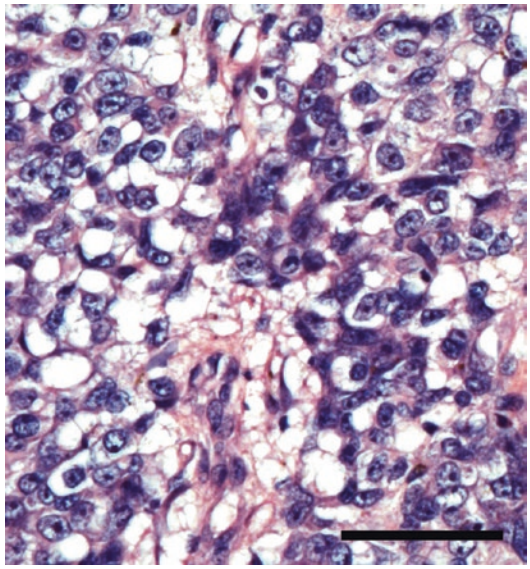

Fig. 15.3 High-power micrograph of a melanoma in the small intestine. Pleomorphic epithelioid tumor cells are seen with large polymorphic nuclei. Mitotic figures are observed (H&E, bar = 50 μm)

S-100, HMB-45, tyrosinase, and Melan-A/Mart-1 [3, 37, 64]. Melan-A with red chromogen may be quite useful in order to separate tumor cells from pigment. A proliferative tumor cell index, such as Ki-67, is highly recommended within the final pathology report. Furthermore, the mutational status regarding *BRAF* and *KIT* genes should be evaluated in order to identify those patients who may be a candidate for select targeted therapy [76].

Staging

There is currently no universal system for the staging of mucosal melanomas [3]. Clark's level is not applicable due to the diverging anatomy and absence of histological landmarks in mucosal membranes compared to skin. The 8th Edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification system suggests a staging system regarding upper respiratory tract melanomas [77]. This classification starts with T3 primary tumors, ignoring smaller T1 and T2 tumors. The AJCC manual suggests both a clinical and pathological staging system for conjunctival melanoma [77]. Apart from the AJCC classification, other systems for head/neck melanoma have been proposed by various authors [65, 78–80].

Tumor thickness seems to be an important prognostic factor in most kinds of melanoma [3, 80, 81]. Ballantyne et al. have suggested a simple three-step staging system that includes stage 1 (localized disease), stage 2 (lymph node involvement), and stage 3 diseases (distant metastases) [79]. Prasad et al. proposed a classification system based upon histological evaluation of tumor invasion that is divided into three distinct tissue compartments, inclusive of melanoma in situ [78]. This system appears to be useful in predicting poor survival for patients with localized, lymph node-negative, and early-stage head/neck melanoma [78]. Another staging system for head/neck melanomas has been proposed by Thompson et al. based on the TNM system. In this system, the presence of distant metastases was the most important factor in predicting patient survival [65]. However, the AJCC classification has been shown to be beneficial in staging sinonasal melanoma [82]. Oral melanomas may be staged according to the AJCC or according to a simple TNM staging system that is combined with a microstaging system of stage 2 tumors, as proposed by Meleti et al. [83].

It has been suggested that the most appropriate staging for anorectal melanoma should allow for some variations of the TNM classification system; however, no true consensus has been agreed upon [24, 84]. The staging for vaginal melanoma primarily utilizes the current AJCC staging system for cutaneous melanoma [85]. Due to the lack of surface keratin and granular layers of the vaginal mucosal membrane, Breslow's thickness should be properly measured from the mucosal surface to the deepest level of invasion within the mucosal membranes [85]. Vulvar melanomas may be staged using the AJCC staging system for cutaneous melanoma [85]. A universal staging algorithm is needed in order to have an accurate method of comparison between tumors of different mucosal origin.

Treatment and Prognosis

The current recommended management of mucosal melanoma is generally based upon physician experience and small cohort studies of treatment, with some difficulty in developing evidence-based treatment guidelines. Although definitive, and often radical, resection has long been the initial treatment of choice, less invasive and morbid procedures have been examined in recent years [6, 22]. There does not appear to be a major difference in survival or clinical outcome between those patients treated with radical surgery and less invasive procedures [3]. A thorough discussion about all possible treatment options with patients and family members is very important, with mutual decision-making based upon the risks and benefits of each treatment modality. The quality of life and associated morbidities of a radical surgery should be discussed in detail before definitive surgery is recommended. The role of lymph node biopsies and/or elective node dissection remains unclear. It is highly advisable to include mucosal melanoma patients in any possible clinical trials utilizing novel, nonoperative therapies, especially those with an advanced tumor stage where surgery may result in significant morbidity and/or disfigurement.

Surgery

Conjunctival Melanoma

Ophthalmologists treat all three melanoma subtypes: uveal melanoma, conjunctival melanoma, and cutaneous melanoma on the eyelids [86]. Conjunctival melanomas represent only 5% of these tumors, and the majority are confined to the sun-exposed bulbar conjunctiva [8, 15]. The treatment of choice is complete surgical resection (*en bloc)* using a no-touch technique with a 3–5 mm surgical margin [17, 34, 87]. To avoid local recurrences, at least one additional treatment modality has to be applied: local brachytherapy, cryotherapy, or local chemotherapy (mitomycin C, interferon alfa-2b, or 5-fluorouracil) [14, 17, 27, 34]. In a large Danish study, patients treated with surgery alone without adjuvant therapy showed an increased risk of both locoregional and distant metastases, with increased risks of melanoma-related and all-cause mortality [14]. Poor prognostic factors include extrabulbar location, increased tumor thickness, nodular appearance, and de novo origin [8, 14, 35]. Local recurrence is very common and is also a poor prognostic sign. Lymphatic spread to regional lymph nodes, as well as to distant sites, such as skin, adrenal glands, brain, and lungs, has been reported [8, 17, 34]. The melanoma-related 10-year mortality rate is approximately 30% [8, 14, 15, 17, 88]. Sentinel lymph node biopsy has been suggested as a safe and feasible procedure in evaluating conjunctival melanoma [89, 90]. However, there is a need for large-scale studies investigating the relationship between a positive sentinel node and ultimate clinical outcome [90].

Mucosal Melanoma of the Sinonasal and Oral Cavity

Melanomas of the mucosal membranes in the head/neck region constitute about 50% of all mucosal melanomas located outside the conjunctiva [2–4]. Surgery remains the gold standard in head/neck mucosal melanoma [2, 3, 72, 73]. The NCCN and the Danish Melanoma Group have produced detailed guidelines regarding head/neck melanoma management [3, 73]. The NCCN treatment guidelines suggest wide surgical resection followed by adjuvant radiotherapy as the treatment of choice regarding AJCC stage T3 and T4aN0 tumors [73]. In addition, the guidelines also suggest some form of neck dissection in cases of a positive lymph node (T3–T4aN1 tumors) [73]. Primary radiotherapy or systemic chemotherapy is recommended for treatment of T4b and T4c tumors [73]. Mutilating procedures are discouraged, and, even with complete resection, recurrence rates of up to 50% are observed. Therefore, some authors advocate considering aggressive adjuvant therapy, regardless of margin status [26, 70].

According to the NCCN guidelines, melanoma of the oral cavity should be managed with wide surgical resection for T3 and T4a tumors [73]. It is suggested that more advanced tumor

stages be managed with primary radiotherapy or systemic chemotherapy [73]. The Danish Melanoma Group recommends primary surgery for all head/neck melanomas, concluding that adjuvant radiotherapy or systemic chemotherapy may be beneficial for local control [72]. However, the use of adjuvant therapy has not been associated with improved survival compared to treatment with surgery alone [11, 43]. An *en bloc* resection should be attempted whenever feasible, with intraoperative frozen section analysis performed for margins whenever possible [33, 73].

Approximately 80% of sinonasal melanomas present as a localized disease, with only a few cases identified as having lymph node or distant metastases at the time of diagnosis [2]. However, up to 50% of patients will present with distant metastases during the course of their disease [2]. A Danish study found recurrence in 72% of patients, regardless of treatment [11]. The 3-year overall survival rate for sinonasal melanoma is about 45%, with a 5-year survival rate of ~30% [11, 26, 91]. The 5-year survival rate of oral melanoma is ~15% [3, 33]. Histologically, confirmed negative resection margins seem to be a positive predictor for survival in head and neck melanomas, but unfortunately this can be technically difficult to achieve due to the complex anatomical structures [11, 26, 43, 91]. Advanced age, multiple tumor sites, presence of necrosis, and amelanotic tumor histology have all been shown to negatively impact long-term survival [26, 37, 43].

In recent years, surgeons have favored the use of endoscopic resection in order to reduce postsurgical morbidity [3]. A recent study found a significantly better survival rate in patients who underwent an endoscopically assisted surgery compared to patients who only received open surgery [92]. Endoscopic resection has not been associated with an increased risk of death compared with more radical surgical procedures, such as craniofacial resection [91]. In general, elective lymph node dissection is not routinely performed or recommended in mucosal melanoma of the head and neck [73]. However, due to a high frequency of lymph node spread in oral melanoma, lymph node dissection may be performed [11].

Mucosal Melanoma of the Anus and Rectum

Approximately 25% of these tumors seem to be without evidence of pigmentation, deemed amelanotic [93]. Due to the fact that a high percentage of cutaneous melanoma patients will present with gastrointestinal metastases on autopsy, all patients with gastrointestinal melanomas should be carefully examined for metastatic disease from a regressed cutaneous melanoma [24, 67]. Aside from the above-mentioned radiological imaging modalities, this includes upper endoscopy, colonoscopy, and video endoscopy of the small bowel in order to exclude metastatic disease. Surgery remains the treatment of choice, but unfortunately no guidelines regarding optimal surgical management exist [3, 24]. Historically, anorectal melanoma has been treated with an abdominoperineal resection, but in recent years the less invasive transanal excision has been favored [22]. The choice of surgical intervention is still controversial and agreement on a gold standard of treatment has not been firmly established. Large, retrospective epidemiological studies have not shown a significant difference in overall survival when comparing the different surgical approaches [22, 24].

Due to the associated postoperative morbidity, transanal excision with free margins should be favored, with more radical procedures such as abdominoperineal resection reserved for those patients where less invasive procedures are not feasible [22]. Histologically free surgical margins seem to correlate with improvements in overall survival [22, 94]. Patients without free margins on transanal excision may be reoperated on, either with a second attempt at transanal excision or with salvage/delayed abdominoperineal resection [22]. Wide local excision has not been shown to alter the median survival time [94]. Patients with perirectal lymph node metastases identified on PET/CT may benefit from curative abdominoperineal resection [24]. The prognosis is particularly poor, with a mean survival time of about 20 months, for both anal and rectum melanoma, regardless of the type of surgical intervention chosen [67].

The overall 5-year survival rate is <20% for rectal melanomas and only 10% when lymph node metastases are present [22]. Some studies suggest a longer median survival (27 months) regarding rectal melanomas [93]. The overall prognosis for anal melanomas (10% 5-year survival) seems to be lower than for rectal melanomas [93]. Recurrence is quite frequent and occurs in about 60% of anal and 70% of rectal melanomas [22, 67, 93]. Presence of distant metastases has a particularly poor prognosis with no long-term survivors beyond 5 years [22]. Negative lymph node status at the time of surgery seems to improve the prognosis, suggesting a role of lymph node resection in the management [22, 67]. However, large-scale studies will be needed in order to guide the development of meaningful treatment protocols. Cases of laparoscopic abdominoperineal resection have been reported, with larger studies needed to further evaluate this technique as a valid operative approach [95].

Melanoma of the Vulva

Most vulvar melanomas are actual cutaneous melanomas, mainly located in non-sun-exposed areas. For many years, the standard treatment of vulvar melanoma was a radical vulvectomy, regardless of tumor size, location, thickness, or level of invasion [7]. However, the overall survival does not seem to improve with radical surgery compared to wide local excision and hemi- or partial vulvectomy [7]. It is advisable to excise a vulvar melanoma with a Breslow's thickness of <2.0 mm with clinical margins of at least 1 cm. Vulvar melanoma with a thickness >2.0 mm should be excised with a 2 cm margin of surrounding skin [28].

The role of lymph node dissection in vulvar melanoma remains controversial [96]. Sentinel lymph node mapping of the inguinal nodal basins by an experienced surgeon is technically feasible, and is currently recommended in the management of vulvar melanoma [28]. Lymphadenectomy may be considered in select patients where palpable or clinically suspicious regional adenopathy is identified [28]. Poor prognostic factors are the presence of ulceration, macroscopic amelanosis, advanced age, Breslow's thickness >2.0 mm, and advanced AJCC stage [96, 97]. In recent years, the 5-year overall survival of vulvar melanoma has improved to about 80% for early-stage tumors [85, 96]. However, recurrence rates are close to 60%, and the 5-year survival rate for more advanced tumor stages remaining at about 30% [28, 96].

Mucosal Melanoma of the Vagina

The optimal surgical approach for vaginal melanoma has not been firmly established. It is evident that patients treated surgically have a better prognosis than those treated without surgery [98]. Vaginal melanoma has historically been surgically managed with forms of "radical" surgery, such as a pelvic exenteration. Unfortunately, "radical" surgery in this case is poorly defined, covering a variety of surgical procedures that range from local excision with total hysterectomy, subtotal vaginectomy, vaginectomy without vulvectomy and total vulvectomy, etc. [99]. Radical surgery has not been proven to increase the long-term prognosis compared to more conservative procedures, and in recent years the treatment of choice has been wide local excision of the primary mucosal melanoma with surgical margin of 1–2 cm [100, 101]. Authors suggest at least a 1 cm margin regarding tumors with a Breslow's depth of <2 mm, and a 2 cm margin for melanomas that are >2 mm in thickness [98]. Furthermore, radical procedures are often associated with an increased morbidity and a decreased quality of life due to the complexity of the operation and close anatomical relationship to the surrounding structures.

Recently, a Japanese group attempted to carry out a systematic review of radical procedures for the treatment of vaginal melanoma, examining whether radical surgery improves the short-term survival and locoregional control [99]. This study introduced a scoring system to classify the grade of radicality in various procedures and concluded that vaginal melanoma patients may benefit from more radical procedures [99]. However, total pelvic exenteration does not seem to significantly increase the overall survival [98]. Larger studies on the effect of radical vs. non-radical procedures are thus necessary. Systemic recurrence contin-

ues to be a major problem, as high as 80% in some studies (80%), metastasizing to the liver and lungs in many instances [98, 100]. Many will present with disseminated disease at the time of initial diagnosis, with a poor 5-year survival rate of ~20% [7, 98]. The role for sentinel lymph node biopsy or elective lymphadenectomy is unclear and possibly considered with each patient, taking into account the associated risks and morbidity associated with complete [28, 98].

Mucosal Melanoma of Other Rare Sites

Due to the very small number of cases of mucosal melanoma confined to other locations than the above mentioned, it is difficult to define the role of different treatment regimens in these tumors. Radical surgery is the treatment of choice regarding melanomas of the larynx, lung, stomach, small and large intestines, biliary tract, uterine cervix, urethra, penis, and urinary bladder [3, 7, 19, 23, 67, 68, 100, 102–106]. However, the prognosis for these rare tumor sites remains extremely poor (see Table 15.1). Most mucosal melanomas may spread to regional lymph nodes at an early stage, but the prognostic role of these metastases remains unknown [102].

Radiotherapy

In general, mucosal melanomas are not considered to be radiosensitive; thus the role and utility of radiotherapy remain unclear [3, 26, 33, 107]. Definitive radiotherapy of head/neck mucosal melanoma has not been shown to significantly benefit patients with respect to local control or overall survival [26, 43, 92, 107]. This may be due to the fact that most patients treated primarily with radiation suffer from an advanced, inoperable tumor stage or that the patient may not be a surgical candidate [26, 107]. A systematic review of head/neck melanoma management concluded that local control rates ranged from 0 to 61% and that overall 5-year survival rates were as low as 13–18% [26].

Authors have reported total radiation dosages exceeding 50 Gy, with no clear association between total dose and overall survival observed [26, 107]. The NCCN treatment guidelines for advanced head/neck melanoma management recommend radiotherapy for gross disease using a conventional fractionation scheme (2 Gy per fraction to a total postoperative dose of 60–66 Gy, possibly up to 70 Gy) [73]. Few studies have compared the effect of conventional fractionation with that of hypofractionation, and the results have been inconclusive [26]. Primary radiotherapy may be attempted for advanced-stage cervical melanoma primarily for palliation of symptoms [100, 108]. Overall, primary radiotherapy should be considered an option in cases of non-operable mucosal melanoma due to significant tumor spread or medical inoperability [7, 26, 107]. It has not been possible to identify an optimal fractionation scheme, with the radiotherapy regimen determined by a radiation oncologist on a patient-per-patient basis [7, 26, 107]. The ability to tolerate the radiation dosage, proximity of the tumor to surrounding critical structures, and overall performance status must be taken into account in all treatment decisions [107].

Adjuvant radiotherapy has been associated with improved local control in mucosal melanomas. However, it does not seem to affect overall survival or the development of distant metastases, regardless of primary tumor location [11, 26, 92, 98, 109, 110]. Some authors suggest that adjuvant radiotherapy is only indicated in head/neck melanoma with negative surgical margins, nodal metastases, and critical structure involvement (i.e., the dura) [91]. Most authors suggest the use of a total dosage exceeding 50 Gy in the adjuvant setting for head/neck melanoma [26]. The role of radiation therapy in anorectal melanoma remains controversial and relatively unknown. Some authors suggest local excision in combination with hypofractionated radiotherapy as a sphincter-sparing alternative to abdominoperineal resection [109]. Adjuvant radiotherapy in combination with surgery may be beneficial compared to surgery alone in the treatment of anorectal melanoma [24]. A large systematic review of genital melanoma suggests that the use of adjuvant radiotherapy in advanced tumor stages may be beneficial in obtaining locoregional control [24]. Conjunctival melanoma may be treated effectively using a

ruthenium^{106}-plaque. The plaque may be used as an adjuvant therapy after surgery [111]. Adjuvant local brachytherapy using a vaginal cesium^{137}-cylinder has also been proposed in vaginal melanoma [7, 101].

Novel Radiotherapy

The role of particle radiotherapy has not yet been firmly established in mucosal melanoma. Due to the poor and inconclusive results of photon radiotherapy regarding survival, particle beam radiotherapy may be a favorable treatment modality of mucosal melanoma in the future. High-dose proton beam therapy has shown some initial promising results in the treatment of head/neck melanoma [112]. A proton beam has the unique physical feature called the Bragg peak, which allows the beam to deposit maximum energy in the tissue at a designated depth [112]. In a Japanese study, 20 patients followed a hypofractionated treatment schedule of 3.5 Gy relative biological effectiveness (RBE) per fraction, administered daily with a total dose of 70 Gy RBE (20 fractions) [112]. In this study, the overall 5-year survival time was 54% and equal to that of surgery [112]. Zenda et al. allocated 32 sinonasal melanoma patients to a hypofractionated scheme administering a total 60 Gy equivalents (GyE) in 15 fractions with a dose fraction of 4 Gy [113]. The 3-year survival in this study was 46% and comparable to conventional photon radiotherapy [113].

Fast neutron radiotherapy is a high linear energy transfer (LET) radiation that has shown to be effective in radioresistant malignancies by generating significant tumor cell death compared to a low LET [26]. Furthermore, the total dose is particularly lower than using photon radiotherapy [26]. Liao et al. reviewed 14 patients treated with fast neutron radiotherapy and found increased locoregional control with a 5-year local control rate of 66% [114]. However, the overall survival was not significantly different, with patients dying due to early distant metastases [114]. Two patients developed serious osteoradionecrosis as an adverse effect [114].

Carbon-ion radiotherapy has both the biological advantage of the high LET from the neutron beam and the same physical properties, and as with proton beam therapy includes the Bragg peak [26]. A Japanese study including 72 head/neck melanoma patients found a 5-year overall locoregional control rate of 84%, with a 5-year survival rate of 39% [115]. Naganawa et al. treated 19 oral mucosal melanoma patients with carbon-ion therapy and found a 5-year local control rate of almost 90% along with an overall survival of 57%, suggesting that carbon-ion radiotherapy is an effective treatment for oral malignant melanoma [116]. A study investigating carbon-ion radiotherapy of gynecological melanoma found a local control rate of 50% and an overall survival equal to surgery, with acceptable adverse effects that were deemed tolerable [117]. These findings suggest that carbon-ion therapy could be a favorable therapy regarding local control in head/neck mucosal melanoma.

Robotic stereotactic body radiotherapy using the CyberKnife® has shown promising results in the treatment of head and neck cancers regarding local control and toxicity [26]. The advantages of the CyberKnife® are the ability to deliver high doses of energy to the tumors and sparing of the adjacent unaffected peripheral tissues and/or organs [26]. Ozyigit et al. reported on four patients with mucosal melanoma treated with the CyberKnife®, two for definitive treatment and two in the adjuvant setting [118]. Three patients demonstrated complete remission and one patient had a partial remission [118].

Chemotherapy

In general, standard chemotherapy and biotherapy have not been shown to be effective in mucosal melanoma. Regimens including various combinations of cisplatin, vinblastine, temozolomide, dacarbazine, interferon-α, or interleukins have been proposed [5–7, 75]. Dacarbazine in combination with interferon-α and interleukin-2 has shown some benefit in head/neck melanoma [9]. Lian et al. found some effect of a regimen combining temozolomide and cisplatin in the postoperative treatment of resected mucosal melanoma [119]. However, the results of these therapies are not so promising regarding mucosal

melanoma, with a considerable risk of developing serious toxic effects [6, 75, 100]. The role of chemotherapy used as preoperative or adjuvant therapy remains unclear because of the lack of consistency in the literature. The patient groups are extremely heterogeneous and the regimens are rarely explained in detail [24].

Targeted Therapy

As previously mentioned, a large fraction of mucosal melanomas seems to harbor amplifications of the *KIT* gene. The KIT inhibitor, imatinib, has been shown to be effective in the treatment of cutaneous melanoma [6, 120]. It also appears that such patients with *KIT* amplifications may benefit from imatinib [6, 121]. Patients harboring aberrations in exon 11 (L576P) or exon 13 (K642E) show better response rates compared to patients having *KIT* amplifications or alterations in other regions [4, 6, 28, 120]. It is advisable to rule out *NRAS* mutation before initiating KIT inhibitor treatment, because an underlying *NRAS* mutation may activate the MAPK pathway downstream of the *KIT* mutation [76].

The BRAF inhibitors, dabrafenib and vemurafenib, have revolutionized the treatment of metastatic cutaneous melanoma [6]. Many authors suggest BRAF inhibition as a promising advance in the treatment of mucosal melanoma. However, the rate of *BRAF* mutations in mucosal melanoma is relatively low, limiting this as a potent treatment option for mucosal melanoma [2, 120]. We recommend screening for *BRAF* mutation, and, if the mutation is present, similar treatment regimens utilized for cutaneous melanoma may be applicable. It is notable that most melanomas will develop resistance to single-agent BRAF inhibition, and a combination with a MEK inhibitor has been shown to increase both disease-free and overall survival [122–124].

Immunotherapy

Treatment with ipilimumab, a monoclonal antibody that blocks the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor, has been shown to impact the overall survival in the treatment of advanced cutaneous melanoma [6, 120]. No randomized trials exist at present for the treatment of mucosal melanoma, but smaller case studies demonstrate a benefit of this agent in treating mucosal melanoma [4, 6]. One such study showed a 12% response rate along with an overall survival time of 4.3–6.4 months [125].

Another novel treatment option is identification of an antibody that blocks the programmed death-1 (PD-1) receptor on activated T cells, which ultimately leads to an enhanced ability of the T cells to eradicate tumor cells. Two PD-1 antibodies, nivolumab and pembrolizumab, have been approved for the first-line treatment of metastatic melanoma [126–128]. Response rates of up to 32% have been identified in mucosal melanoma, which are comparable to those found in cutaneous melanoma [129]. Thus, it is clear that checkpoint inhibition therapy has become a promising treatment option in mucosal melanoma, with further studies planned for the future. A large, pooled analysis of data for anti-PD-1 therapy in combination with ipilimumab in mucosal melanoma has shown that this combination has a synergistic efficacy when compared to each given alone. However, combination therapy was associated with high rates of grade 3 or 4 adverse effects [127]. Given the fast development of novel agents, these must be studied in large, multicenter studies of mucosal melanoma.

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