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Review Article

Primary mucosal melanomas: a comprehensive review

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Abstract: Primary mucosal melanomas arise from melanocytes located in mucosal membranes lining respiratory, gastrointestinal and urogenital tract. Although a majority of mucosal melanomas originate from the mucosa of the nasal cavity and accessory sinuses, oral cavity, anorectum, vulva and vagina, they can arise in almost any part of mucosal membranes. Most of mucosal melanomas occur in occult sites, which together with the lack of early and specific signs contribute to late diagnosis, and poor prognosis. Because of their rareness the knowledge about their pathogenesis and risk factors is insufficient, and also there are not well established protocols for staging and treatment of mucosal melanomas. Surgery is the mainstay of treatment, with trends toward more conservative treatment since radical surgery did not show an advantage for survival. Radiotherapy can provide better local control in some locations, but did not show improvement in survival. There is no effective systemic therapy for these aggressive tumors. Compared with cutaneous and ocular melanoma, mucosal melanomas have lowest percent of five-year survival. Recently revealed molecular changes underlying mucosal melanomas offer new hope for development of more effective systemic therapy for mucosal melanomas. Herein we presented a comprehensive review of various locations of primary melanoma along mucosal membranes, their epidemiological and clinical features, and treatment options. We also gave a short comparison of some characteristics of cutaneous and mucosal melanomas.

Keywords: Mucosal melanoma, gastrointestinal, respiratory, urogenital

Introduction

Melanomas are malignant tumors arising from pigment cells - melanocytes. Although melanoma is mostly of cutaneous origin, it can also occur in various extracutaneous sites where pigment cells are present. Extracutaneous melanomas include ocular melanomas, mucosal and leptomeningeal melanomas, and rare cases of melanoma originating in some internal organs.

Primary mucosal melanomas arise from melanocytes located in mucosal membranes lining respiratory, gastrointestinal and urogenital tract. Although the majority of mucosal melanomas originate from the mucosa of the nasal cavity and accessory sinuses, oral cavity, anorectum, vulva and vagina, they can arise in almost every part of mucosal membranes. Mucosal melanomas are rare, but they are known to behave more aggressive and have less favorable prognosis compared to other melanoma subtypes. Most of mucosal melanomas occur in occult sites, which together with the lack of early and specific signs contribute to late diagnosis, and poor prognosis. Because of their rareness our knowledge about their pathogenesis and risk factors is insufficient, and also there are not well established protocols for staging and treatment of mucosal melanomas.

Herein we presented a comprehensive review of various locations of primary melanoma along mucosal membranes, their epidemiological and clinical features, and treatment options. We also gave a short comparison of some characteristics of cutaneous and mucosal melanomas.

Melanocytes in mucosal membranes

Melanocytes arise from the neural crest, a transitory embryological structure induced in the phase of gastrulation at the dorsal borders of the neural plate [1]. Melanocyte precursors

Table 1. Distribution of melanocytes in mucosal membranes

Site	Reference
Oral cavity	[3]
Esophagus	[4]
Rectum and anal canal	[5, 6]
Nasal cavity and paranasal sinuses	[7, 8]
Larynx	[9]
Vagina	[10]
Cervix	[11]

migrate from neural crest through embryonic mesenchyme along characteristic pathways to their final destination in the human body. Most of melanocytes in vertebrates are located in the epidermis and dermis of the skin, but they are also found in many other locations including eye, mucosal membranes and leptomeninges [2]. **Table 1** shows distributions of melanocytes along various mucosal membranes in humans.

Melanocytes are considered to be pigment cells with the primary function of pigmentation and UV protection in the skin and eye. But, it is the fact that melanocytes are present in many sun-shielded sites in the body, including mucosal membranes, in which they are not needed for sun protection. Although the presence of melanocytes has been demonstrated in many mucosal membranes, the function of mucosal melanocytes is not understood. There are evidences supporting other, non-pigment, functions of melanocytes such as antimicrobial and immunological functions [12, 13]. Melanocytes have phagocytic and possibly antigen-presenting function, and also produce various cytokines [12, 13]. Their location in the superficial layer of skin together with their presumable immunological functions make them highly likely to be part of innate immune defense system [12, 13]. Melanocytes in mucosal membranes which are like skin "immunologically critical surfaces", could also be involved in antimicrobial defense.

Epidemiology

Unlike cutaneous melanoma, which is estimated to be the fifth most common cancer in the United States among men, and the sixth among women [14], mucosal melanomas are rare. They represent only about 1.4% of all melanomas [15]. In contrast to cutaneous melanoma which incidence is increasing [16] incidence of mucosal melanoma is believed to remain stable [17]. In the US, its rate is 2.2 mucosal melanoma cases per million per year compared to 153.5 for cutaneous melanomas [15]. Mucosal melanomas show higher rates among women compared to men (2.8 vs. 1.5 per million) [15]. Female predominance is mostly caused by higher rates of genital tract melanomas which account for 56.5% of mucosal melanomas among them, while there is no difference in rates between genders for extragenital mucosal melanomas [15].

Incidence of mucosal melanomas is increasing with age; more than 65% of patients are older than 60 years, and less than 3% are younger than 30 years [15]. Rates of mucosal melanomas are approximately twice higher among whites than among blacks [15]. Although exists, this difference in rates between whites and blacks is less pronounced compared to cutaneous melanoma (16:1) [15], but comparable to that of conjunctival melanoma (2.6:1) [18], which arise from the only mucosal membrane exposed to sun radiation. Cutaneous melanoma has higher rates in costal and southern states in the US but, the same was not observed for mucosal melanoma [15].

Etiopathogenesis

Risk factors for development of mucosal melanomas have not been identified. Since this type of melanomas arise on surfaces which are not exposed to sun, this well-known risk factor for cutaneous melanoma is unlikely to be implicated. Several studies did not show association of human papilloma viruses, human herpes viruses, and polyomavirus with etiopathogenesis of mucosal melanomas [19-21]. Exposure to formaldehyde was suggested as a risk factor for sinonasal mucosal melanoma, since there were reported cases of this rare malignancy among workers professionally exposed to this substance [22, 23]. For oral mucosal melanoma cigarette smoking was suggested as risk factor, because it has been demonstrated that oral pigmented lesions are more prevalent among smokers [24].

Although, all melanocytes share the same embryologic origin, microenvironment in their final destinations in different sites in the body differs a lot. Epidermal and dermal melanocytes, as well as melanocytes of the mucosal

membranes and uvea, are situated in different kinds of tissues and surrounded by different types of cells. According to that it can be expected that they also differ in adhesion molecules or signal pathways involved in their growth and maintenance, and consequently in development of melanoma. In a relation to that, Aoki et al. suggested the existence of two distinct types of melanocytes in mouse based on differential signaling requirement for the maintenance of noncutaneous, and dermal versus epidermal melanocytes [25].

Recent genetic studies revealed that different melanoma subtypes carry different genetic mutations. While cutaneous melanomas frequently carry oncogenic mutations in BRAF (serine/threonine kinase) [26, 27], BRAF mutations have been only rarely found in mucosal melanomas [28, 29]. However, Curtin et al. [29] showed that mucosal melanomas in 39% of cases carry mutations and/or increased copy number of KIT (receptor tyrosine kinase). Beadling et al. [30] found KIT mutations in 15.6% of mucosal melanomas. Another subtype of melanomas, uveal melanomas carry activating mutations in either GNAQ or GNA11 genes in more than 80% [31, 32]. Differences in underlying genetic mutations between different melanoma subtypes suggest that those tumors probably represent distinct biological entities, beside their differences in clinical features.

Revealing the differences between melanocytes situated in different tissues in the body, as well as revealing alternative functions of these cells, might be of importance in understanding melanomagenesis in different tissues.

Diagnosis

When diagnosing primary mucosal melanoma, especially in some sites on which it rarely arise, it is of crucial importance to exclude possibility of metastatic lesion from primary cutaneous or ocular melanoma. If we take into account possibility of unknown or regressed primary cutaneous melanoma, establishing of diagnosis becomes even more challenging.

When there is no history of previous melanoma, the whole-body skin examination and ophthalmic examination are crucial to exclude the presence of cutaneous or ocular primary melanoma at the present time.

Presence of in situ melanoma or radial growth phase is important for distinguishing primary lesions from metastases [33]. Allen and Spitz [34] defined as main criteria for diagnosis of primary melanoma junctional or in situ melanoma component with intact epithelium overlaying invasive melanoma. However, because of hidden location and lack of early symptoms, diagnosis of mucosal melanomas is usually delayed and many lesions are ulcerated at diagnosis, so this criterion is not easy to assess. Because of that, the absence of junctional change in an ulcerated lesion does not preclude the possibility that the lesion is a primary melanoma [34]. Amelanotic appearance which is not rare among mucosal lesions, makes diagnosis even more difficult. Macroscopically pigmented lesions are always highly suspect for melanoma, but when pigment is absent even microscopically diagnosis is difficult. Immunohistochemical staining positive for protein S-100, HMB-45, Melan-A, Mart-1 and tyrosinase support diagnosis of melanoma.

Staging

There is no universal staging system for mucosal melanomas. Various staging systems are in use for various locations, usually staging systems which are in use for other more common malignancies of a particular anatomic site. However, in the seventh edition of The American Committee on Cancer (AJCC) cancer staging manual, it was given tumor–node–metastasis (TNM) staging system for mucosal melanoma of the head and neck [35]. Establishment of appropriate staging systems for other locations of mucosal melanoma is needed. That would provide adequate staging, planning of treatment and prognostication for patients, but also allow meaningful comparison of outcome-results from various institutions in order to define best treatment options.

Mucosal melanomas of the respiratory tract

Primary mucosal melanoma in the respiratory tract is most common in the nasal cavity and paranasal sinuses, while it extremely rare occurs in the mucosa of larynx or tracheobronchial tree. On the other hand, lung is very common site for metastatic melanoma from prima-

ry cutaneous, ocular or other primary mucosal site [36-38].

Mucosal melanoma of the nasal cavity, paranasal sinuses and nasopharynx is rare entity and accounts for about 4% of all sinonasal malignancies [23]. Incidence of nasal cavity melanoma is 0.3 per million, and for paranasal sinuses 0.2 per million [15]. Melanocytes were found to be normally present in mucosa of sinonasal cavity in about 21% of individuals [8].

Nasal cavity is predominant location accounting for about 80% of melanomas in sinonasal tract [39, 40]. Most common sites of origin within the nasal cavity are septum and lateral wall [40], and among paranasal sinuses maxillary and ethmoid sinus [39-41]. Melanoma of sinonasal tract mostly occurs in elderly, with a mean age at presentation 64.3 years [23].

The most common symptoms are unilateral nasal obstruction, mass lesion, and epistaxis [23]. In advanced stages pain and facial distortion can occur, and rarely proptosis and diplopia. It is infrequently diagnosed accidentally because of its occult location, and patients with epistaxis usually refer to physician earlier than those with obstructive symptoms. Macroscopically, majority of tumors appear as polypoid, brown or black pigmented mass, often ulcerated. Tumors can also be amelanotic, mimicking other more common tumors. Patients with larger size of tumor (>3cm) are associated with poorer prognosis [23].

Surgical treatment remains the treatment of choice for sinonasal melanoma, although complete surgical removal is often limited by surrounding structures, so negative margins are not easy to achieve. There was not found statistically significant difference in overall survival between patients treated by surgery alone, or patients treated with surgery and radiotherapy or chemotherapy, or combination of all three treatment modalities [23]. Although postoperative radiotherapy has not shown improvement in overall survival [23, 41-43], it can provide better local control [41-44]. Local recurrence affects about half of patients, and in the majority of cases it is a predictor of distant metastases [40].

Five-year survival rates range from 25% to 42% [23, 41, 45]. Patients with nasal melanoma have a better prognosis than those with sinus melanoma. In pooled data of 203 patients from five series, five-year survival for patients with nasal melanoma was 31% compared to 0% for those with sinus melanoma [40]. Most common sites for distant metastases are lung, liver and bones [23]. Negative predictive factors for survival are infiltration of surrounding structures, location in maxillary and ethmoid sinus, subtotal resection, non-polypus form, and distant metastases [46], as well as nasopharyngeal location of tumor, age > 60 years, recurrences, undifferentiated histology and presentation with obstructive symptoms only [23].

Mucosal melanoma of the larynx is extremely rare tumor with about 60 cases reported in the medical literature [47]. Presence of melanocytes was observed in normal laryngeal mucosa [9], so although it is uncommon, origin of primary mucosal melanoma in larynx is possible. Most patients with laryngeal melanoma are in sixth and seventh decade, and about 80% are males [47, 48]. It mostly occurs in supraglottic region and true vocal cords [47-49]. The most common presenting symptom is hoarseness, followed by throat irritation [47]. Other presenting symptoms include sore throat, dysphagia, neck swelling, and pain. Complete surgical removal is the primary treatment, with or without adjuvant radiotherapy and/or chemotherapy. Local recurrence is less common compared to other mucosal melanomas of the head and neck region [47]. Despite the treatment, prognosis is very poor. About 80% of patients have regional or distant metastases at time of diagnosis, and five-year survival is less than 10% [47]. In the literature review of Terada et al. [47], of 28 patients for whom data were available only 2 survived more than five years.

Primary melanoma of the lung is exceptionally rare tumor with about 30 cases reported in literature [50, 51]. Presence of melanocytes in tracheobronchial tree has not been demonstrated, and origin of primary melanoma of the lung remains obscure. One possible explanation lies in embryology. Respiratory system develops as a tubular downward outgrowth from the primitive foregut posed between areas which will later become the oral cavity above and the esophagus below it [52]. Since the presence of melanocytes have been demonstrated in the oral cavity and esophagus, struc-

tures that have common embryologic origin with respiratory tract, and even more in upper respiratory tract, it is possible that during development melanocytes also migrate in tracheobronchial mucosa. Melanoma often metastasize in lung, and metastatic lesions are mostly multiple, unlike primary lesions which are solitary. Since majority melanoma lesions in the lung are metastatic, strict clinical and pathological criteria must be complied to exclude extrapulmonary primary lesion.

In the literature review of Ost et al. [53] which included 19 cases, mean age at the time of diagnosis was 54 years (ranging from 29-90 years), with no gender preference. Clinical presentation included cough, hemoptysis, postobstructive pneumonia, lobar collapse or atelectasis, and in about 30% of patients tumor was incidentaly observed on chest radiography [53, 54]. Endobronchial growth is common and can often be seen on bronchoscopy as pigmented or non-pigmented mass. Peripheral lesions are rare. Lobectomy or pneumonectomy are treatment of choice, and complete lymph node resection is also advised. Role of adjuvant radio and chemotherapy remains to be determined.

Mucosal melanomas of the gastrointestinal tract

Primary mucosal melanoma can arise in any site of gastrointestinal mucosa, but it is most common in anorectal (31.4% in the anal canal, and 22.2% in the rectum) and oropharyngeal region (32.8%), while esophagus (5.9%), stomach (2.7%), small bowel (2.3%), gallbladder (1.4%), and large bowel (0.9%), are extremely rare sites of origin [55]. Approximately 50% of patients with primary gastrointestinal melanoma are older than 70 years, and 14% are younger than 50 years [55]. Majority of patients are Caucasians, about 95% [55]. In the study of Cheung et al. which included 659 primary melanomas of gastrointestinal mucosa location of tumor, advanced tumor stage, failure to undertake surgical resection, positive lymph node status, and age have been found to be independent predictors of poorer outcome [55]. Most gastrointestinal lesions are metastatic, and small intestine, colon, and stomach are the most common sites of metastases [56, 57]. Because of that, metastatic melanoma from another primary site must be ruled out when these sites of rare occurrence are involved.

Mucosal melanoma of the oral cavity is a rare tumor with incidence of 0.2 per million [15]. It is more frequent among Japanese people [58, 59] and accounts for 7.5 % of all melanomas in contrast to cutaneous melanoma which is less common among them [58]. Oral melanomas originate from melanocytes normally present in oral mucosa [3]. It has been demonstrated that density of melanocytes in the lower lip is increasing with age, and that increase is significantly higher in men [60]. Some authors reported more common occurrence of oral melanoma in men [39, 40, 61]. It is most common among elderly, with a mean age of 59.2 years (range 16 to 91 years) [62].

Oral melanoma mostly arise de novo, but in about one third of patients it develops from pre-existing melanocytic lesion [39, 58, 63]. It can occur in any site of the oral cavity, but palate, especially hard palate, and maxillary gingiva are most common sites [39, 40, 58, 59]. Other sites include mandibular gingiva, labial and buccal mucosa, and extremely rare floor of the mouth, tongue, tonsils, uvula and parotid gland [39, 59, 62]. Initially, tumor is usually asymptomatic, presenting as flat, macular, or slightly elevated and irregular pigmented lesion. In later course symptoms as swelling, ulceration, bleeding, pain and tooth mobility can occur, and lesion can become elevated. Satellite lesions and areas of pre-existing melanosis can be present around lesion [64]. Amelanotic tumors are not rare, and absence of pigment delay diagnosis and contribute to worse prognosis [65]. Regional lymph node metastases are present in 25% of patients with oral melanoma [66].

Surgery is the main treatment option, and can be combined with adjuvant radiotherapy and chemotherapy, but despite all, prognosis remains poor. Local failure occurs in about half of patients [66]. Radiotherapy improves local control in mucosal melanomas of the head and neck region, but does not improve survival [42, 44].

Five-year survival for oral melanoma is very poor 12.3-16.6% [39, 40, 59], with a median survival about 2 years [39]. Gingival location carries better prognosis compared to palatal

(median survival 46 vs. 22 months) [39]. Involvement of lymph nodes affects survival considerably, with a median survival being 46 months, when lymph nodes are not involved, and 18 months when they are involved [39]. Increased tumor thickness increases risk for regional and distant metastases, and tumors > 4mm have high metastatic potential [39].

Benign pigmented lesions of the oral mucosa, melanocytic or non-melanocytic, are not rare, so they require adequate differential diagnosis. Differential diagnosis of oral melanoma includes melanosis, melanotic macule, oral nevi, racial pigmentation, smoking-associated melanosis, postinfammatory pigmentation, amalgam tattoo, medication melanosis, melanoacanthoma, Peutz-Jeghers syndrome, Addison's disease and Kaposi's sarcoma [39, 63].

Considering poor prognosis of these tumors, any pigmented lesion of the oral mucosa deserve attention. Biopsy, and even prophylactic excision of some lesions can be advised, having on mind fact that one third of oral melanomas develop from pre-existing melanocytic lesions.

Mucosal melanoma of the esophagus is a rare tumor with total of 337 cases reported in world literature by 2011, and accounting only 0.1-0.2% of all esophageal malignances [67]. Presence of melanocytes in esophageal mucosa was first demonstrated by De La Pava in 1963 [4]. Ohashi et al. [68] have found melanocytes in 7.7% of normal esophagus specimens in Japanese, and in 29.9% of cases with esophageal carcinoma. They found that melanocytes are mostly located in the lower part of esophagus, and that their number is increased in areas of hyperplastic epithelium and chronic esophagitis. Melanoma of the esophagus is in the majority of cases located in the middle and lower part of esophagus [69, 70], only in about 10% of cases location is upper third of esophagus [69]. About a half of cases of esophageal melanoma, reported in the literature, are among Japanese [70]. Most patients are in sixth and seventh decade of life, with male to female ratio 2:1 [69]. Presenting symptoms include dysphagia, as the most common symptom, retrosternal pain, weight loss, and rare common, hematemesis and melena. On upper gastrointestinal endoscopy it usually presents as elevated, pigmented, rarely ulcerated lesion, and sometimes surrounded with satellite lesions. In 10-25% of tumor is amelanotic [71]. Radical surgical treatment remains the treatment of choice, and provides the best hope for survival, while adjuvant therapy mainly has palliative role [55, 70, 72]. Five-year survival reported by Sabanathan et al. [69] in 1989 was only 4.2%. Cheung et al. [55] analysed 659 cases of primary gastrointestinal melanomas (from 1973 to 2004), of which 39 were esophageal, and they reported median survival of 12 months, and five-year survival of 14% for esophageal melanomas. Volpin et al. [73] analysed 25 cases reported in literature from 1989 to 2000 and calculated five-year survival of 37 %.

Primary melanoma of the stomach is extremely rare tumor, with less than 20 cases reported in the literature. Since the presence of melanocytes in the epithelium of the stomach and intestines has not been demonstrated, origin of melanoma in these sites remains obscure. Presenting symptoms described in the literature are unspecific and include abdominal pain, weight loss, upper gastrointestinal bleeding and anemia [74, 75], but it has been reported asymptomatic case presenting only with axillary lymphadenopathy [76]. Primary gastric melanoma has very poor prognosis with a median survival of only 5 months, compared to 17 months for all primary gastrointestinal melanomas [55].

Primary melanoma of the small intestine is extremely uncommon, but this is the most common location of metastatic gastrointestinal melanoma [56, 57]. Presence of melanocytes has not been demonstrated in the small intestine, and origin of primary melanoma of the small intestine remains unknown. One of possible explanations is that primary melanoma of small intestine origin from melanoblasts which migrate to the distal ileum through the omphalomesenteric canal [77]. Some authors question the existence of primary melanoma of the small intestine, suggesting that all melanomas in the small intestine are metastases from unknown or regressed primary cutaneous melanoma [78]. In a review of 18 cases of small intestine melanoma, ileum was most common location (83%), mean age at the time of diagnosis was 54 years, and 75% had mesenteric lymph node metastases [79]. Presenting symp-

toms are non-specific and include nausea and vomiting, anorexia, abdominal pain, weight loss, gastrointestinal bleeding with secondary anemia, invagination with obstructive symptoms. Prognosis of melanoma of the small intestine is poor, with a median survival of 16 months [55]. Surgery is the main treatment option, but no significant improvement in survival was observed for surgical extirpation of tumors located in small intestine [55].

Anorectal mucosal melanoma is the most common among primary melanomas of the gastrointestinal tract [55], and third most common location after cutaneous and ocular. It accounts for 16.5% of all mucosal melanomas and has incidence rate of 0.4 per million [15]. Presence of melanocytes was demonstrated in normal mucosa of the rectum and anal canal [5, 6]. Clemmensen et al. [6] found melanocytes commonly present in the anal squamous zone, only sporadically in the anal transitional zone, and not at all in the colorectal zone. However, in the epithelium surrounding resected primary anal melanomas, increased numbers of benign melanocytes were demonstrated not only in the squamous and transitional zone, but also in the colorectal zone [6]. Anorectal melanoma most common occurs between 65-70 years, shows female predominance [15, 80, 81], and it is 1.7-fold higher among whites than among blacks [80]. Cote and Sobin [80] has observed increase in incidence of anorectal melanoma, with an 1.8-fold increase comparing period 1973-1987 with 1988-2003. This finding is similar to that of cutaneous melanoma, which has shown 1.4-fold increase during the same period [80]. Authors suggested that the rise in incidence might be because of true increase in incidence but also because of development of specific staining for melanoma markers which provided more accurate diagnosis.

Lesions can affect anal canal, rectum or both, but the great majority of tumors is located within 6cm of the anal rim [82]. The most common symptoms of anorectal melanoma are rectal bleeding, anorectal pain or discomfort, and prolapse of tumor mass at anus. Tumor is usually polypoid with or without pigmentation, and also it can be ulcerated [83]. Amelanotic tumors appear in about 30% of patient [84], and together with polypoid nature of the lesion and unspecific symptoms contribute to misdiagnosis. Anorectal melanoma is misdiagnosed in about two thirds of patients and most often as hemorrhoids, adenocarcinoma, polyps, and rectal cancer [82, 85]. At the time of diagnosis, about one third of patients have regional or distant metastases [81, 86].

Abdominoperineal resection was for a long time considered as the initial treatment for anorectal melanoma. However, recently some studies demonstrated that abdominoperineal resection, as more extensive operation, has not shown an advantage for survival compared to wide local excision [81, 85, 87, 88]. Since wide local excision avoids need for colostomy and cause less morbidity, and there is no advantage for survival, it is suggested as the initial treatment of choice [85]. Although, local recurrence is more common among patients treated with wide local excision, it does not affect survival [85, 89, 90]. Radiotherapy after local excision provides better local control but does not improve survival [91]. Lymph node involvement affects survival significantly, with a median survival for patients with localized disease being 24 months compared to 17 months for patients with lymphatic metastases, and five-year survival 26.7% compared to 9.8% [81]. Because of that Iddings et al. [81] suggested selective lymphadenectomy in management of anorectal melanoma. Most common sites of distant metastases are liver and lung [38].

Despite all treatment modalities, overall five-year survival for anorectal melanoma remains poor, about 20% [17, 85, 90], and median survival 14-20 months [82, 88].

Hemorrhoids are benign and common disease, often neglected by both the patient and physician, and because of that misdiagnosing of anorectal melanoma as hemorrhoids seriously affects prognosis [82]. Patients with anorectal melanoma misdiagnosed as hemorrhoids have one-year survival of only 29%, and median survival of only 6 months [82]. Since the most lesions are located near the dentate line, digital examination could detect the mass in the most of cases. In order to establish correct and prompt diagnosis, digital examination should be performed in patients with those unspecific complaints, and suspected hemorrhoids. Since tumor can be amelanotic in approximately one third of patients, absence of pigment does not exclude diagnosis, and in that cases biopsy is helpful, not only for early diagnosing of anorec-

tal melanoma, but it also contribute to early diagnosis of other malignancies of anorectum.

Primary melanoma of the colon is exceptionally rare tumor with 12 cases reported to date [92]. Mean age of patients on presentation is 60.4 years, with no gender predilection. In most reported cases tumors were located in the right colon and cecum [92, 93], but the location in the transverse colon was also reported [93]. Abdominal pain and weight loss were most common complains [92]. Colonoscopy is most reliable procedure for initial diagnosis, and surgical resection the mainstay of treatment.

Primary melanoma of the biliary tract is extremely rare and can arise in the gall bladder or bile duct. Only 9 cases of primary melanoma of bile duct were reported in the literature [94], and 30 cases of primary gallbladder melanoma [95]. In the series of 659 cases of primary gastrointestinal tract melanoma there were only 9 from gallbladder, but they demonstrated longest median survival (41 months compared to 17 months for all primary GIT melanomas) [55]. Presenting symptoms are like in biliary tract calculosis or cholecystitis, including obstructive jaundice pain in right upper quadrant of abdomen, itching and dark urine [94, 96]. The vast majority of biliary tract melanomas are metastatic, and tend to present as multiple, flat pigmented lesions, while primary tumors present as solitary, polypoid lesion on gross examination, and have junctional in situ component [94, 96].

Mucosal melanomas of the urogenital tract

Although rare, melanoma can arise in almost any part of the urogenital tract, including vulva and vagina, uterine cervix, urethra and urinary bladder. Mucosal melanomas of the urogenital tract are more common among women. Female genital tract accounts for 18% of all mucosal melanomas, and urinary tract melanomas for about 3% [17]. Among female genital tract, the most common is vulvar melanoma (76.7%) followed by vaginal (19.8%), while cervical melanoma is least common [15].

Vulvar melanoma is the second most common malignancy of the vulva, after squamous cell carcinoma [97], but is still rare with incidence of 0.1 per 100 000 females per year [98]. Although vulvar melanoma arises on hairy and glabrous skin of the vulva, because of its sun shielded location and continuity with vaginal mucosa it is mostly described with mucosal melanomas.

Vulvar melanoma mostly occurs in older women, with a median age 68 years, and in almost 90% of cases occurs in the white race [97]. Most common sites of origin are clitoral area and labia majora, followed by labia minora and periurethral area, while vaginal introitus is the least common [99]. Vulvar melanomas are more common in glabrous skin, involving 46% of cases, compared to 12% emerging in hairy skin, while in 35% it extends to both areas [99]. The most common presenting symptoms are bleeding, lump or vulvar mass, pruritus, pain or irritation, miction discomfort and discharge [99, 100]. Amelanotic tumors are common in glabrous skin (about 39%), while in hairy skin of vulva, they are rare [99]. Satelite lesions are also common and occur in 22% of patients, and in some cases, preexisting nevi can be present on hairy skin of vulva [99].

Age, stage and lymph node involvement were found to be significant for survival in vulvar melanoma [97]. In patients with positive lymph nodes five-year disease specific survival is 24%, compared with 68.3% for those with negative lymph nodes [97]. In a population-based study of 219 women, multivariate analysis showed that, for stage I patients (clinical three-stage system), tumor thickness, ulceration, and clinical amelanosis were independent predictors of poor survival [101]. Surgery is the main treatment option for vulvar melanoma. There are trends toward less extensive resection, since there have not been found a difference in survival rates between patients treated with radical compared to conservative surgery [102].

Melanoma of the vagina is very rare, with less than 300 cases reported in literature, and accounts for less than 3% of all vaginal malignances [103]. Melanocytes were found in the basal layer of vaginal epithelial surface in 3% of women [10]. Vaginal melanoma is mainly a disease of elderly women, and predominantly occurs in white individuals. It most commonly affects postmenopausal women (80%), and mean age at diagnosis is around 60 years [104, 105]. Vaginal melanoma most often occurs in the lower third and anterior wall of vagina [103].

The most common presenting symptoms are vaginal bleeding and discharge, presence of mass lesion, and less common pain [104]. Macroscopically it presents like variably pigmented lesion, fragile and easily bleeds on touch. In more than half of patients tumor was found ulcerated [106]. Amelanotic appearance is rare, but can easily be misdiagnosed for other malignances [107]. In about 20% of cases, disease is multifocal [105]. Size of tumor appears to be the most predictive for survival, and tumors <3cm in size have better survival [104, 108]. In the literature review of Buchanan et al. [108], median survival for tumors ≥3 cm was 12 months compared with 41 months for size <3 cm. On the other hand, tumor thickness did not significantly affect survival [104, 108]. Patients with positive lymph nodes have significantly lower median survival compared with patients with negative lymph nodes (7.8 vs. 30 months) [105]. Local recurrence is frequent and appears in about 40% of patients [104]. Surgery is the best available treatment for vaginal melanoma, and recent publications have shown that radical surgery does not show an advantage over conservative surgery [102]. Wide local excision followed, by radiotherapy is appropriate for many patients, but when it is not possible, exenteration is reasonable [102]. Most common sites of distant metastases are lung, liver and bones [104, 105]. Prognosis of vaginal melanoma is poor regardless therapy, and reported five-year survival rates are ranging from 0 to 21% [104-106, 109-111].

Melanoma of the cervix is exceedingly rare with about 80 cases reported in the literature [112]. Over 60% of women are older than 50 years at the time of diagnosis [112, 113]. Majority of patients are symptomatic on diagnosis, with vaginal bleeding being the most common symptom followed by vaginal discharge [113]. Inspection usually shows variably pigmented exophytic cervical mass, but amelanotic appearance is also possible. Majority of patients are diagnosed in early stage [113], but despite that prognosis remains poor, and only 10.7% of patients survive more than five years [112]. Treatment is like for cervical carcinoma including radical surgery, while radiotherapy and chemotherapy mostly have palliative role [102].

Melanoma of the urethra is very rare tumor and account for about 4% of all urethral malignancies [102]. Distal urethra is the most common site of occurrence of melanoma in urinary tract [114, 115]. It mostly occurs in elderly patients, and more common in females [115]. In about one fifth of patients tumor is amelanotic, which together with polypoid growth can be easily misdiagnosed for urethral polyps, caruncle, mucosal prolapse, chancre or urothelial tumors [116]. Urethral melanoma shows high rate of local recurrence, about 60% at 1 year [114]. Overall survival in a series of 11 women at 3 years was 27% [114]. Surgery is the main treatment option, but optimal extent of surgery remains undefined [102].

Melanoma of the urinary bladder is extremely uncommon with about 20 cases reported in the literature. Most patients are over 50 years old [117]. Most common presenting symptoms are hematuria and dysuria, but when symptoms occur, tumor is usually locally advanced [117]. Diagnosis is usually made by cystoscopy and tumor biopsy, but in one reported case it was made by cytologic examination of urine [118]. Surgery is the main treatment for urinary bladder melanoma, but the prognosis is poor. Metastatic melanoma of the urinary bladder is also rare [119], but always has to be excluded before establishing diagnosis of primary tumor.

Comparison of mucosal and cutaneous melanomas

All melanomas originate from melanocyte, but despite common cellular origin tumors originating from skin, and extracutaneous sites show many differences. The most obvious difference is in rates, with cutaneous melanoma being far most common type of melanoma, while it rarely origin in other sites in the body where pigment cells are present. Sun radiation, major risk factor for cutaneous melanoma, cannot be associated with mucosal melanomas, which arise in sun-shielded sites. Differences are also present in age, gender and racial distribution, survival rates, and also recently revealed differences in molecular changes. **Table 2** shows a comparison of some characteristics of cutaneous and mucosal melanoma.

Perspectives

Better understanding of genetic changes in mucosal melanoma could provide development of more effective, targeted therapeutic agents.

Table 2. Comparison of cutaneous and mucosal melanoma

	Cutaneous	Mucosal
Rate per million [15]	153.5	2.2
Males vs. females rate per million [15]	193.7 vs. 125.2	1.5 vs. 2.8
Percent of all melanomas	91.2% [17]	1.4% [15]
Trends in incidence	Rising [16]	Stable [17]
Risk factors	UV light	Unknown
Mean age [17]	55.3 years	67 years
Race [15]	White 94-96%	White 0.7-2.1%
	Black 81-89%	Black 4.7-13.4%
White:black ratio [15]	16:1	2:1
Most common sites of distant metastases	skin (13–38%)	lung (54%)
	distant lymph nodes (5–34%)	liver (35%)
	distant subcutaneous tissues (32%)	bones (25%)
	lung (18–36%)	[38]
	liver (14–20%)	
	CNS (2–20%)	
	bones (4–17%)	
	[36]	
Five-year survival [17]	80.8%	25%
Treatment [17]	91.5% surgery only	57% surgery only
		19% surgery + radiotherapy

Discovery of KIT-activating mutations in mucosal melanoma provided a hope that KIT-inhibitors, such as imatinib and sunitinib, could be effective therapeutic agents against this aggressive disease. Some studies reported response on KIT-inhibitors in patients with mucosal melanoma and KIT aberrations. Hodi and colleagues [120] reported major response on treatment with imatinib in a case of KIT-mutated rectal melanoma. Minor and colleagues [121] reported one case of complete remission for 15 months, and two partial responses (lasting for 1 and 7 months) in patients with KIT-mutated tumors treated with sunitinib. Rarity of mucosal melanomas and the fact that KIT mutations are present only in some patients make it difficult to conduct large clinical trials. Discovery of different genetic mutations in different subtypes of melanoma, but also presence of different mutations within the same subtype, leads to new, molecular, classification of melanomas. Together with development of targeted therapeutic agents, this could provide specific treatment for patients in accordance with underlying molecular changes present in the particular tumor.

Conclusions

Primary mucosal melanomas are very rare but aggressive tumors. Compared with cutaneous (80.8%) and ocular melanomas (74.6%), mucosal melanomas have the lowest percent of five-year survivals, only 25% [17]. For now, best hope for survival offers early detection and complete surgical removal. However, because of occult site of occurrence and unspecific symptoms, diagnosis is usually delayed. Each anatomical site requires specific surgical approach, and in many cases complete removal of tumor is limited by surrounding structures. Extent of surgery needed for adequate local control is still controversial. Radiotherapy can provide better local control, but does not improve survival. Role of chemotherapy and immunotherapy is not clear. Recently revealed genetic changes underlying mucosal melanomas offer new hope for development of more effective systemic therapy for these aggressive tumors. Since risk factors are not well known, improvement of prevention seems not possible. Any pigmented lesion on mucosal membranes and mucocutaneous junctions deserves attention. It is very important that clinicians have on mind these rare sites of occurrence of melanoma, especially because some of them are accessible for examination, such as oral or genital tract, and could be detected at an earlier stage.

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