6 Anorectal Melanoma

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Abstract: Anorectal melanoma (AM) is a rare malignancy, characterized by aggressive behavior and a poor prognosis. AM is more frequent in female patients aged over 50 years. AM accounts for 0.4–1.6% of all melanomas, 23.8% of all mucosal melanomas, and 1% of all anorectal malignant tumors. There are many theories regarding AM pathogenesis. Some consider that AM may be related to oxidative stress in the region and/or to immunosuppression. Others propose that AM may derive from Schwannian neuroblastic cells or cells of the amine-precursor uptake and decarboxylation system of the gut. Assessment of pigmented lesions located on hidden areas is difficult. Together with late and nonspecific signs and symptoms which usually occur only in conjunction with large masses, diagnosis of these mucosal melanomas is often delayed. Most frequently, the signs and symptoms are obstruction, rectal bleeding, pain, or rectal tenesmus. There are various histological variants of AM: epithelioid, spindle cell, lymphoma-like, and pleomorphic. Surgery (abdominoperineal resection or local excision) is the most

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effective treatment for AM; however, this is not associated with improved overall survival. Recurrence is more frequent in cases of anorectal and rectal involvement when compared with anal-only involvement. There is currently no consensus about the most appropriate systemic treatment. The efficacy of some protocols previously used in patients with cutaneous melanomas is currently being studied in mucosal melanoma.

Key words: Anorectal; Gastrointestinal; Malignancy; Melanoma; Mucosal

INTRODUCTION

Anorectal melanoma (AM) is a rare malignancy which is often difficult to diagnose due to the hidden site. This malignancy is characterized by aggressive behavior, and patients often have a very poor prognosis, which is related to the frequent delay in the diagnosis, as well as biological differences in malignant melanocytes of this anatomic area compared to other sites. Since AM accounts for only 1% of all anorectal malignant tumors (1), few studies of AM have been conducted, with few available data for physicians and for researchers. Correct and early diagnosis, with subsequent multidisciplinary management, is important for improving the quality of life and prognosis of these patients (1). In this chapter, we investigate the main epidemiological, pathophysiological, genetic, clinical, and pathological features of AM, as well as therapeutic options.

EPIDEMIOLOGY

In 1857, Moore reported the first case of AM (2). The US National Cancer Database stated that mucosal melanoma represents the third most common site of primary melanomas after the skin and eye, and the anorectal canal is the second most frequent mucosal site for melanoma after the head and neck (3, 4). Compared to cutaneous melanoma (CM), primary gastrointestinal melanoma is extremely rare. The most common gastrointestinal localization is the anorectal tract (>50%), followed by the stomach, small intestine, and colon. It is important to highlight that the rectal localization is more frequent than the anal; nevertheless, the two entities are studied together. AM accounts for 0.4–M accounts for 0.4was and represents 23.8% of all mucosal melanomas (1). It is more frequent in females compared to males (2:1 ratio) and the mean age at diagnosis is 54.5 years (5).

There is a lower incidence of mucosal melanomas in dark-pigmented individuals, possibly related to the antioxidant properties of melanin rather than its photo-screening effects (Table 1) (6). According to Micu et al. (3) and Ragnarsson-Olding et al. (7), although the incidence rate of CM has increased in recent decades, the incidence of AM has remained constant. Ragnarsson-Olding et al. found that the age-standardized incidence of AM was stable between 1960 and 1999, at approximately 1.0 and 0.7 per million in females and males, respectively, in contrast to an increasing incidence of CMs (7). Micu et al. demonstrated that the incidence rate of AM in Norway was 0.48 per million in the period between 1987 and 2007 and 0.35 per million in the period between

TABLE 1 Epidemiology of primary mucosal melanoma

Primary mucosal melanoma	Case/million/year
Conjunctival	0.5/million/year
Sinonasal	0.5/million/year
Anorectal	0.4/million/year
Oral	0.2/million/year

1966 and 1986. This difference was not statistically significant. In contrast, the incidence rate of CM increased from 103 per million between 1966 and 1986, to 217 per million between 1987 and 2007 ($P < 0.001$) (3).

In Queensland, Australia, which has the highest incidence rate of CM in the world, Miller et al. (8) did not find any significant differences in the incidence rate of AM compared to other geographical regions (8). Increased incidence of AM has been reported in some regions of the United States in recent years, perhaps due to some other etiological factors like HIV infection (4). Overall survival of this AM is poor, with a 5-year overall survival ranging between 10 and 20%, which is thought to be a consequence of late diagnosis (4).

PATHOGENESIS AND GENETICS OF AM

Melanocytes migrate from the neural crest or from the mucocutaneous junctions to the cutis (9–11). However, although melanin synthesis is the principal function of melanocytes, its role in mucosal areas is mainly characterized by antioxidant activity and contributing to the regional immune response (9–11). Accordingly, the malignant transformation in anorectal areas may be related to oxidative stress in these regions and/or to immunosuppression. This is also explained by the observation that AM often arises in patients aged >50 years (9). However, other valid theories have been postulated, describing that AM, as well as gastrointestinal melanoma, may derive from Schwannian neuroblastic cells of the autonomic intestinal innervation system or from the cells of the amine-precursor uptake and decarboxylation (APUD) system of the gut. APUD cells are involved in the uptake of precursors of biologically active amines, production of active amines through subsequent intracellular decarboxylation, and storage of the amine product in secretory vesicles (10). Their developmental lineage derives from neuroectoderm. During embryogenesis, the upper part of the embryonic plate (ectoderm) develops into skin and nervous tissue, while the lower part (endoderm) forms the gut lining and structures branching off this lining (5, 10). A part of the ectoderm (neural crest) which flanks the region forming the spinal cord and brain contains cells that migrate through the embryo to form various structures, including the skin (5, 10). Four APUD cell types have been described: β cell (secreting insulin), PP cell (secreting pancreatic polypeptide), α cell (secreting glucagon), and δ cell (secreting somatostatin) (10).

Melanocytes are detected normally in the anal squamous zone and, sporadically, in the anal transition zone. This localization is probably linked to the presence of melanocytes in the epithelial lining of the dentate line, which extends proximally to the rectum. Another valid theory is the hormonal one. Indeed, a higher female incidence has been reported in extracutaneous melanoma and in AM, potentially due to the involvement of estrogens in the pathogenesis of melanoma. However, there is no solid evidence regarding the role of female sex hormones in melanoma risk. Notwithstanding, estrogens are known to increase the number of melanocytes and modify their melanin content (9, 12–15).

Melanoma of shield sites and of extracutaneous sites is not influenced by ultraviolet (UV) radiation (9, 16–20). The absence of stem-cell niche in the bulge region in melanomas of glabrous skin could explain the pathogenesis of this malignancy in this anatomical region. These melanomas demonstrate aggressive behavior regardless of diagnostic delay. In this regard, other factors such as biological differences between melanocytes of this anatomical region and cutaneous melanocytes could play a crucial role in the pathogenesis of mucosal melanoma. Furthermore, UV radiation, probably via its role in vitamin D photosynthesis in exposed skin, may have a systemic protective effect against melanomas. However, in a recent study, we found a decrease of vitamin D receptor (VDR) in shield-site melanomas compared to nonshield-site melanomas (as chronically sun-exposed anatomic sites or intermittent sun-exposed areas) (16), and lower serological levels of vitamin D in patients with shield-site melanomas, compared to nonshield-site melanomas (19). All these findings confirm that other pathways are involved in the pathogenesis of shield-site melanomas, as well as in noncutaneous melanomas.

GENETICS

Because of the rarity of primary mucosal melanoma (PMM), its genetic basis is still unclear. As reported by several authors (21–24), PMM shows distinctive characteristics in comparison with CM. As reported by Edwards et al., no exon 15 *BRAF* mutations has been detected in a series of 13 PMM (23), while a mutation rate of 33% in CM has been described in the literature (21). Furthermore, in a recent review by Ascierto et al., it has been reported that the *BRAF* mutation rate was only 3% in PMM (24). This finding suggests that the prevalence of *BRAF* mutations in melanoma could depend on the anatomical origin of the tumor, probably in direct relation to the extent of sun exposure (23). Furthermore, the absence of $BRAF^{V600E}$ mutations suggests that the BRAF inhibitors (as vemurafenib and dabrafenib) would not be effective in the treatment of PMM (24). It has also been reported that oncogenic mutation in the *NRAS* gene is rarely described in PMM, while it has been detected in 19–28% of CM (24). Furthermore, mutations in *GNAQ* and *GNAII* have been described as important triggers in melanoma pathogenesis, but they have been rarely described in PMM (24). Moreover, PMM shows a low frequency of *KIT* mutations (7–8%) and cyclin D1 amplification (10%) but at the same time a high rate of *c-Myc* amplifications (62.5%) (22).

It has been speculated that human papilloma virus (HPV) could lead to a higher genomic instability in PMM, supporting the degradation of the p53 protein. However, Dahlgren et al. evaluated with PCR the presence of HPV DNA

in 15 AM, detecting no HPV DNA in these specimens (25), thereby concluding that the 36 HPV-tested subtypes did not play a pivotal role in the development of AM (25). It has also been speculated that human herpesvirus (HHV)-8 could be involved in the pathogenesis of PMM and specifically in AM, because of the production of IL-6 by the virus. Indeed, IL-6 plays a central role in stimulating the proliferation of melanoma cells (26). However, the analysis of Helmke et al. detected no involvement of HHV-8 in developing melanoma of the anorectal area (27). Indeed, HHV-8 DNA was not found in 12 AMs by the specific and highly sensitive PCR assay (27).

A small rate of *BRAF*^{V599E} mutation, which occurs up to 75% in CM, has been reported in PMM (<10%) (28). *BRAF*, which is located on chromosome 7q34, encodes a serine/threonine kinase, regulating proliferation and differentiation via the MAPK pathway. The V599E mutation causes the hyperactivation of BRAF kinase activity. As reported by Helmke et al., BRAF exon 15 mutation has been not detected in AM (29). Edwards et al. also detected no *BRAF* exon 15 mutation in 13 PMM, including 4 AM (23). These findings corroborate the evidence that PMM does not share molecular features with CM. Furthermore, the lack of *BRAF* mutations in PMM suggests that the *BRAF* mutations in melanoma are influenced by the extent of sun exposure. In addition, as reported above, these findings suggest that BRAF/MEK inhibitors may not be useful in the therapy of PMM, as well as for AM (23).

It has been reported that up to 40% of AM shows *KIT* mutation (21). This percentage is higher than that reported in melanoma of the head/neck, as described by Beadling et al. (30). However, Antonescu et al. found only 23% of *KIT* mutation in AM (31). c-KIT plays a pivotal role in growth, differentiation, migration, and proliferation of melanocytes. It is also involved in activation of several cellular signaling pathways, including the phosphoinositide 3-kinase/AKT, mitogen-activated protein kinase, Janus kinase, leading to cancer progression and extension. Most of *KIT* mutations in PMM occurred within exon 11, which encodes the juxtamembrane domain of the *KIT* receptor. Furthermore, a minority of mutations were detected also in the exon 17, which encodes the tyrosine kinase-2 domain of *KIT* (31). In addition, Omholt et al. reported *BRAF* mutation in 4.5% of AM and *NRAS* mutation in 4.5% of AM (32). However, no impact of *KIT* and *NRAS* mutations on clinical outcome has been reported by these authors (31, 32). In contrast, Kong et al. demonstrated reduced survival in melanoma patients with *KIT* mutations in a large-scale analysis (33). In a study conducted on 44 specimens, Satzger et al. reported *KIT* mutations in 86% of AMs (34). The high percentage of mutation was observed in the juxtamembrane area of *KIT*, encoded by exons 11 and 13, which probably led to the activation of c-KIT. The authors detected no influence of *KIT* mutations on both disease-free and overall survival (34). As reported by several authors, therapeutic c-KIT blockade could be useful in the treatment of PMM patients with activating KIT mutation (35–37). More precisely, Antonescu et al. reported that 15% of AM show the c-KIT L576P mutation that is particularly associated with sensitivity to imatinib *in vitro* (31). Therefore, the evaluation of c-KIT mutations in PMM patients could be extremely useful, although the role of this mutation in the prognosis is still under debate.

Furthermore, Omholt et al. reported that mutations in the *KIT*, *NRAS*, and *BRAF* genes did not lead to activation of the ERK and Akt pathways in PM,

suggesting that other mechanisms, including mutation of the *PIK3CA* oncogene (encoding the catalytic subunit p110ms, including mutation of the ill under debate. KIT mutation in *PTEN* tumor suppressor gene may promote the activation of the ERK and Akt pathways in PMM (30). In contrast to CM, RAS mutation, especially in codon 61 of the *NRAS*, is rarely detected in AM. Indeed, it has been demonstrated that elevated level of *NRAS* mutations were linked to UV radiation (38).

CLINICAL FEATURES AND INSTRUMENTAL DIAGNOSIS

A self-assessment of the skin plays a pivotal role in the early diagnosis of melanoma. However, when pigmented lesions are located on hidden areas, their assessment becomes more difficult. Accordingly, due to the hidden location and lack of early symptoms, the diagnosis of AM is usually delayed, with a poor prognosis. According to a recent European study involving 444 patients with mucosal melanomas, AM was associated with the poorest prognosis (39). In this study, the authors related this poor prognosis to a propensity of AM to develop distant and brain metastases (39).

The main reasons that lead to a diagnosis of AM are the late and nonspecific signs and symptoms, which occur usually when tumoral masses are large (3–4 cm) (40, 41), and when the neoplasia involves the rectum, anus, or both sites, extending within 6 cm from the anal rim (40, 41). The most common clinical presentations of AM are changes in bowel habits, bowel obstruction, rectal bleeding, anal pain, and/or rectal tenesmus. These features are often associated with a mass that can prolapse through the anus (40, 41).

Clinically, AMs are polypoid lesions, mostly ulcerated and not pigmented, with an irregular surface, sometimes showing black or brown spots (Figure 1) (42). AM is often bloody and covered with mucinous/fibrinous material. The frequent amelanotic presentation of AM means that neoplasms of other origins, such as non-Hodgkin lymphoma, adenocarcinoma, and sarcoma, should be considered in the differential diagnosis (42). Nevertheless, due to the nonspecific clinical manifestations reported by the patients, AM is often misdiagnosed, masquerading as more common diseases of the lower gastrointestinal tract (such as adenomatous polyps, hemorrhoids, or rectal ulcers), resulting in delayed diagnosis (42). For these reasons, the lack of a clinical specificity for AM requires accurate and objective instrumental investigations, including rectal examination and investigations such as endoscopic ultrasonography and proctosigmoidoscopy. It is important to emphasize that there are no standardized diagnostic protocols for AM, unlike other common neoplasms of the large intestine (43).

Considering the lack of standardized diagnostic protocol for investigating possible AM, as there are for colorectal cancer, the identification of more appropriate and accurate diagnostic methods would allow for greater diagnostic accuracy and improvement of sensitivity and specificity of the endoscopic investigations. In this regard, proctosigmoidoscopy allows for macroscopic identification and characterization of the mass. A suspicion of AM is usually present in case of a mucosal lesion that invades the dentate line, and which has brown and dark spots on the surface. In the absence of the abovementioned potential diagnostic criteria (melanin is present in only 30% of cases), histologic and immunohistochemical

Figure 1 **Anorectal melanoma.** Courtesy of Dr. Fabrizio Gabrielli.

evaluation (using HMB-45, S-100, Melan-A, and Vimentin) are indicated. In this regard, many authors emphasize the importance of performing multiple biopsies in order to avoid inconclusive histological characterizations (2, 9).

Finally, it is emphasized to use endoscopic ultrasounds and magnetic resonance imaging (MRI), to supplement colonoscopy in preoperative settings, allowing for the evaluation of the bowel wall in all five layers, assessing tumor infiltration, radial extension, and the total thickness of the neoplasia (2, 9). Ultrasonography allows the possibility for immediate biopsy in order to characterize suspicious loco-regional lymph nodes.

PATHOLOGY

As reported above, because of hidden location and lack of early symptoms, diagnosis of a mucosal melanoma is usually delayed, and many lesions are ulcerated at the time of diagnosis, which associates with worse prognosis. It can also be difficult to differentiate between primary and metastatic disease. Usually, the absence of junctional changes in an ulcerated lesion does not preclude the possibility that the lesion is a primary melanoma (42, 44). In this regard, the typical amelanotic appearance of many AMs makes the diagnosis even more difficult (42, 44). Indeed, while pigmented lesions of the anorectal tract are always

highly suspect for melanoma, when pigment is absent, even microscopically, the diagnosis is more difficult and only an immunohistological examination can help reach a diagnosis.

There are four histologic types of AM. These include the epithelioid AM, the spindle-cell AM, the lymphoma-like AM, and the pleomorphic AM (44). The mitotic rate is usually about 2.82 mitotic figures per high-power field, ranging between 0.5 and 5.5 per high-power field, and without showing a correlation with the morphologic features or pigmentation (44).

The lymphoma-like AM, the spindle-cell AM, and the pleomorphic AM are often confused with a nonmelanocytic malignancy. Indeed, spindle-cell AM can be easily misdiagnosed for a gastrointestinal stromal tumor of the rectum. For this reason, an accurate immunohistochemical analysis plays a pivotal role in the diagnosis of AM.

On immunohistochemistry, the cell population of AM usually shows a strong positivity to S100—a protein highly sensitive for melanocytic differentiation. However, given the lack of specificity, it is used primarily as a screening tool. Indeed, S-100 is present in many conditions, including nerve sheath tumors, gliomas, neuroendocrine cells, melanocytic proliferations, some histiocytic proliferations, langerhans cells, and also rarely in poorly differentiated carcinomas. AM usually stains for Melan-A, tyrosinase, and HMB-45, although there is often a variability in strength and distribution (44). HMB-45 and Melan-A also stain other tumors with melanocytic differentiation (e.g. angiomyolipomas, lymphangioleiomyomatosis, and clear-cell myomelanocytic tumors); regardless, they have high specificity for melanocytic lesions, although their sensitivity is lower than S100. In fact, Melan-A and HMB-45 commonly fail to stain spindle-cell melanoma, often leading to diagnostic pitfalls (44). For the same reasons, anti-tyrosinase antibodies, although they are considered melanocyte-specific (targeting the tyrosinase enzyme needed early in the cascade to create melanin pigment), are uncommonly present in cutaneous spindle-cell-type melanomas.

Usually AM is negative for pan-cytokeratin. Accordingly, it is important to remember that up to 10% of melanomas can show an expression of a keratin and/or epithelial marker (above all CAM5.2 and epithelial membrane antigen) (44). Accordingly, a misdiagnosis with a poorly differentiated rectal carcinoma is possible. Finally, another pitfall may be the positivity to carcinoembryonic antigen when using polyclonal antibodies (44). Finally, c-Kit is positive in about 75% of AMs. c-Kit is a transmembrane tyrosine kinase receptor that plays a role in the development and proliferation of melanocytes, above all in mucosal sites (44).

STAGING

For a long time, AMs, as well as the other primary gastrointestinal melanomas, have been considered as metastatic melanomas (15). In fact, as reported above, the diagnosis of primary AM is often difficult to perform. However, some caution can aid in accurate diagnosis.

In order to consider a gastrointestinal melanoma as a primary melanoma, the following points must be satisfied: the presence of atypical melanocytes along the

basal epithelium in a histological sample, the absence of melanomas elsewhere, no history of metastatic melanoma, no previous regressed melanocytic lesions, negative history for skin lesion previously removed without histological examination, negative ophthalmological examination, negative esophagogastroduodenoscopy, negative colonoscopy (ignoring the suspect anorectal lesion), negative genital examinations, and negative oropharyngeal and rhinopharyngeal examinations (18).

After reaching the diagnosis of primary AM, it is important to remember that AM has a poor overall survival (5 years; 10–20%). This is unchanged over the years due to the rarity of the neoplasm, which inhibits the development of standardized diagnostic and therapeutic protocols. Regardless of poor prognosis, AM is also related to various factors, including perineural invasion, rectal wall infiltration, nodal involvement, and distance metastases. In 2013, Bello et al. examined the clinical relevance of the location of origin of AM as a prognostic factor and, in a sample of 96 patients (41 with anal melanoma, 32 with AM, and 23 with rectal melanoma), found that lesions distal to the dentate line were more likely to recur with lymph-nodal involvement, which may represent differences in nodal drainage. However, the authors concluded that there were no differences in the long-term prognosis, which remained poor for all cases of AM (45). At present, there is no staging available for primitive mucosal melanomas of the gastrointestinal tract which provides prognostic value.

Generally, the growth of AM closely resembles the nodular pattern of its cutaneous counterpart. This feature explains it poor survival and several reports have corroborating data that link survival most closely with tumor thickness. Patients with AM with a thickness ≤2 mm have better survival than patients with lesions >2 mm (46, 47). Regarding tumor size, Goldman et al. found a correlation between overall survival and tumor size, showing greater overall survival for patients with tumors ≤2 cm (48). Unfortunately, because of the typical delay in the diagnosis, the vast majority of AM presents to clinicians as large, polypoid tumors with a thickness >2 mm, a tumor size >2 cm, and nodal involvement. According to these considerations, Breslow depth alone is of little use in the staging of the majority of primary AM. The relative consequences are that most authors advocated continued use of the clinical staging system developed for CM, where stage I is clinically localized disease, stage II is regional lymph-nodal disease, and stage III is disseminated disease (46–51). However, two alternatives, based on the 7th American Joint Committee on Cancer (AJCC) staging system, might be applicable to AM: tumor node metastasis (TNM) staging of rectal cancer (rectal TNM) and tumor node metastasis of anal canal cancer (anal TNM) (52). Rectal TNM is based on the depth of tumor invasion into or beyond the wall of the rectum (T), number of regional lymph nodes involved (N), and status of distant metastases (M) (52). Anal TNM differs from rectal TNM in terms of tumor size (T) and status of regional or systemic LN involvement (N) (52). Staging systems for AM are summarized in Table 2.

Mucosal infiltration is critically related to the presence of lymph nodes metastases (>40%) and, consequently, to distant metastases, especially in the lung and in the liver (>90% in case of nodes neoplastic involvement). In 2006, Podnos et al., in a study of the Surveillance, Epidemiology, and End Results (SEER) database, found that in 126 AMs the extent of disease was statistically related with the poorest overall survival among mucosal melanomas (53). Recently, Iddings et al. found that lymph-nodal involvement is an important prognostic feature in AM (50). At

TABLE 2 Classifications of anorectal melanoma (AM)

Thickness (46, 47)	Tumor size (48)	General staging (46)	Anal AM* (52) T[a], N[b], M[c]	Rectal AM* (52) T[d], N[e], M[c]
		Stage 1: clinically localized	I = T1, N0, MO	I = T1, 2 N0, M0
≤2.00 mm	≤2.00 cm	Stage 2: lymph-nodal involvement	II = T2, 3 N0, M0	IIA/B/C = T3/4a/4b, N0, M0
≥2.01 mm	≥2.01 cm	Stage 3: disseminated disease	IIIA = T4, N0, M0 or T1, 2 ,3, N1, M0 IIIB = T4, N1, M0 or T1, 2, 3, N2, M0	IIIA = T1, 2, N1, 1c, M0 or T1, N2a, M0 IIIB = T3, 4a, N1, 1c, M0 or T2, 3, N2a, M0 or T1, 2, N2b, M0 IIIC = T4a, N2a, M0 or T3, 4a, N2b, M0, or T4b, N1, 2, M0
			IV = Any T, Any N, M1	IV = Any T, Any N, M1

*Reclassification of TNM system according to Chae et al. (52)

AM classification according to TNM staging of anal cancer based on the 7th American Joint Committee on Cancer (AJCC) staging system: (a)T1 ≤ 2.00 cm; T2 ≥ 2.01 cm and ≤5.00 cm; T3 ≥ 5.01 cm; T4, invades other organs;(b) N1, metastasis in perirectal lymph node; N2, metastasis in unilateral internal iliac and/or inguinal lymph node; N3, metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes; (c) M, distant metastases.

AM classification according to TNM staging of rectal cancer based on the 7th AJCC staging system. (d) T1 invades submucosa, T2 invades *muscularis propria*, T3 invades into perirectal tissues, T4a penetrates to the surface of the visceral peritoneum, T4b invades to other organs; (e) N1a, metastasis in one regional lymph node; N1b, metastasis in two to three regional lymph nodes; N1c, tumor deposit; N2a, metastasis in four to six regional lymph nodes; N2b, metastasis in seven or more regional lymph nodes; (c) M, distant metastases.

the same time, Chae et al., while attempting to develop a classification system for AM, highlighted and confirmed the predictive value of the number of regional lymph nodes involved (52). Unfortunately, detection of lymphatic drainage in the anal region is particularly difficult, due to the presence of 10 different lymphatic pathways. Inguinal/iliac or perirectal lymph nodes are most commonly involved in AM. Consequently, 18F-FDG-PET/CT and contrast-enhanced CT have been mainly studied for the evaluation of loco-regional and systemic involvement in AM patients. In this regard, PET/CT is superior for staging these patients, especially for loco-regional and systemic neoplastic involvement, and to plan the best surgical treatment for individual cases.

TREATMENT

The literature reports surgery as the most effective treatment for AM. However, assuming an adequate preoperative staging, which accurately highlights localization of the disease, surgery does not result in real improvement of the overall survival. Indeed, there is no evidence regarding the benefits of surgery types. Many authors underline that abdominoperineal resection (APR) does not appear to be associated with improved survival compared to a local excision; on the contrary, APR seems to be related to a better disease-free survival with major control of loco-regional disease but without effectiveness in metastatic disease (54, 55). Long-term outcome does not seem to be influenced by the extent of surgical excisions and, in many selected cases, local excisions are recommended in order to improve quality of life. APR has been compared to a wider excision in some studies; one of these, evaluating a database of 143 patients, did not find any survival differences in patients treated with the two different surgical procedures (55). Tumors with thickness ≤1 mm can undergo local sphincter-saving resection with 1 cm margin, and tumors with thickness between 1.01 and 4 mm can undergo local sphincter-saving resection with 2 cm margin.

The role of regional lymphadenectomy in the surgical treatment of AM is a subject of debate (20). Mesorectal, pelvic sidewall, and inguinal lymph nodes are at increased risk of involvement from anorectal lesions. For this reason, during APR, the mesorectal lymph nodes are resected together with the primary tumor (20). However, contrary to Goldman et al., Yeh et al. found that nodal involvement in AM did not predict outcome in patients undergoing radical resection (56). At the same time, bilateral inguinal lymphadenectomy in AM patients without palpable lymph nodes did not improve survival but increased the risk of complications. While elective lymph-nodal dissection should be considered only in case of clinically palpable disease (20), laparoscopic abdominal-perineal resection can also be considered a feasible choice in case of respectable primary melanoma and clinically palpable lymph node metastases (55). Local primary disease control could be reached with adjuvant radiotherapy after surgical definitive resection and wide excision; on the contrary, loco-regional lymph node irradiation is controversial; indeed, this procedure seems to be related to a worsening of postoperative lymphedema (55).

Regarding systemic therapies, there is currently no consensus about the most appropriate treatment for this type of melanoma. Some protocols, previously

directed to patients with CMs, have been studied in the context of mucosal melanoma, including AM. Traditional chemotherapy seems to have similar efficacy to chemo-immunotherapies in terms of survival. Dacarbazine (a cytotoxic chemotherapy) is associated with a survival of 20% (20). However, many responses are partial, with a median response duration of only 4–6 months (20, 57). There are no standardized data supporting a survival benefit for dacarbazine 250 mg/m^2/day intra venous (repeating the cycle every 3 weeks) versus placebo (20, 57). The analogue of dacarbazine and temozolomide (with the dosage of 200 mg/m^2/day orally for 5 days, repeating the cycle every 4 weeks) has the benefit of being available orally, showing also a lower rate of central nervous system relapse (20). Dacarbazine or temozolomide, in association with other agents, has demonstrated no advantage over single-agent chemotherapy in phase III trials (58). A multicenter case–control study, evaluating the effect of dacarbazine versus a four-drug combination known as Dartmouth regimen (dacarbazine, cisplatin, carmustine, and tamoxifen), showed that the Dartmouth regimen exhibited a marginally improved response rate (19%) over dacarbazine alone (10%), but without statistical significance. Regardless, both treatments showed a poor survival of 7 months (58). Finally, Singhal et al. reported the effectiveness of taxanes (as paclitaxel at 100 mg/m^2/IV) + platinum (cisplatin at 20 mg/m^2 IV or carboplatin 2 mg/mL/min IV) with or without the use of metronomic therapy, showing a median overall survival of 11 months (59).

Other treatments of historical significance consisted of immune mediators, such as interferon-α and interleukin-2 (IL-2). High dosages of IL-2 (consisting of 22 mcg/kg, 33 mcg/kg, 36 mcg/kg, or 44 mcg/kg every 8 h for up to 14 consecutive doses or doses as clinically tolerated) showed a good response in metastatic CM (60). High doses of IL-2 can be performed as monotherapy or in combination with the conventional chemotherapy. Indeed, recently, IL-2 combined with ipilimumab (at 3 mg/kg) showed effectiveness in AM patients with unresectable disease (60, 61).

With the advent of targeted therapy, a higher number of therapeutic choices are available; however, the treatment of AM remains an important challenge. As reported above, up to 40% of AM presents *KIT* mutation. Accordingly, identifying c-Kit mutation allows initiation of treatment with tyrosine kinase inhibitors (62). Sorafenib (400 mg orally twice daily) is a less specific antagonist on c-Kit than imatinib but has been shown to have some effect in a previous case report of AM (63). Subsequently, Knowles et al. found an improvement in metastatic AM patients treated with imatinib (400 mg orally twice daily until disease progression or unacceptable toxicity), concluding that patients with AM and with a positivity to c-Kit mutation could be considered for a treatment with tyrosine kinase inhibitors (TKIs) (63). However, in case of brain metastases, the use of sorafenib and imatinib is not recommended, as these TKIs do not cross the blood–brain barrier. In these cases, it is advised to use dasatinib (100 mg twice daily), a potent c-Kit inhibitor, which has a better penetration in the central nervous system (7).

Currently, association of anti-BRAF antibody (as vemurafenib or dabrafenib) and MEK inhibitors (as cobimetinib or trametinib) are available for BRAF-positive metastatic CM; however, there are no data for metastatic AM. Because the percentage of AM with *BRAF* mutation is low, the use of vemurafenib and dabrafenib in AM is not currently a pivotal therapeutic option.

In 2016, Tan reported the case of a young man with a metastatic AM, treated with ipilimumab, who showed improvement of 5-months, until the patient showed signs of disease progression (64). Immune-checkpoint inhibitors such as

ipilimumab (antibody to cytotoxic T-lymphocyte-associated protein-4, CTLA4), nivolumab (anti-PD1 antibody), and pembrolizumab (anti-PD1 antibody) have been approved for the treatment of melanoma. Tokuhara et al. reported a successful treatment with nivolumab in a 67-year-old Japanese man with metastatic (liver and bone) AM. The authors administered nivolumab at 2 mg/kg, showing a significant reduction of liver and bone metastases, showing no recurrences after 17 months of follow-up (65). Nivolumab and more generally anti-PD1 treatments seem to be a promising choice for the treatment of metastatic AM. Combined chemotherapy, anti-BRAF therapy, TKIs, and immune-checkpoint inhibitors remain important therapeutic options for these patients (65, 66).

CONCLUSION

AM is a rare and aggressive malignancy. Patients usually present with advanced disease due to delayed diagnosis and intrinsic high aggressiveness of the malignancy. Because of the rarity and biological heterogeneity of the malignancy, there is neither a standardized staging schema nor a standardized medical and/or surgical therapy. Although combined chemotherapy, anti-BRAF therapy, TKIs, and immune-checkpoint inhibitors remain important therapeutic options for these patients, further studies are needed to improve survival and quality of life of AM patients.

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REFERENCES

1. Schaefer T, Satzger I, Gutzmer R. Clinics, prognosis and new therapeutic options in patients with mucosal melanoma. A retrospective analysis of 75 patients. Medicine (Baltimore). 2017 Jan;96(1):e5753. http://dx.doi.org/10.1097/MD.0000000000005753
2. Parra RS, Almeida AL, Badiale BG, Moraes MM, Rocha JJ, Féres O. Melanoma of the anal canal. Clinics (Sao Paulo). 2010 Oct;65(10):1063–1065. http://dx.doi.org/10.1590/S1807-59322010001000026
3. Micu E, Juzeniene A, Moan J. Comparison of the time and latitude trends of melanoma incidence in anorectal region and perianal skin with those of cutaneous malignant melanoma in Norway. J Eur Acad Dermatol Venereol. 2011 Dec;25(12):1444–9. http://dx.doi.org/10.1111/j.1468-3083.2011.04023.x
4. Cagir B, Whiteford MH, Topham A, Rakinic J, Fry RD. Changing epidemiology of anorectal melanoma. Dis Colon Rectum. 1999;42:1203–1208. http://dx.doi.org/10.1007/BF02238576
5. Postow MA, Hamid O, Carvajal RD. Mucosal melanoma: Pathogenesis, clinical behavior, and management. Curr Oncol Rep. 2012 Oct;14(5):441–8. http://dx.doi.org/10.1007/s11912-012-0244-x

6. Dominiak NR, Wick MR, Smith MT. Mucosal melanomas: Site-specific information, comparisons with cutaneous tumors, and differential diagnosis. Semin Diagn Pathol. 2016 Jul;33(4):191–7. http://dx.doi.org/10.1053/j.semdp.2016.04.003
7. Ragnarsson-Olding BK, Nilsson PJ, Olding LB, Nilsson BR. Primary ano-rectal malignant melanomas within a population-based national patient series in Sweden during 40 years. Acta Oncol. 2009;48(1):125–31. http://dx.doi.org/10.1080/02841860802120861
8. Miller BJ, Rutherford LF, McLeod GR, Cohen JR. Where the sun never shines: Anorectal melanoma. Aust N Z J Surg. 1997 Dec;67(12):846–8. http://dx.doi.org/10.1111/j.1445-2197.1997.tb07609.x
9. Jensen C, Kin C. Black is the new black: Prolapsing primary anorectal melanoma. Dig Dis Sci. 2017 Nov;62(11):2991–3. http://dx.doi.org/10.1007/s10620-017-4527-9
10. Bharti K, Nguyen MT, Skuntz S, Bertuzzi S, Arnheiter H. The other pigment cell: specification and development of the pigmented epithelium of the vertebrate eye. Pigment Cell Res. 2006 Oct;19(5):380–94. http://dx.doi.org/10.1111/j.1600-0749.2006.00318.x
11. Zecca L, Zucca FA, Wilms H, Sulzer D. Neuromelanin of the substantia nigra: A neuronal black hole with protective and toxic characteristics. Trends Neurosci. 2003 Nov;26(11):578–80. http://dx.doi.org/10.1016/j.tins.2003.08.009
12. Karagas MR, Zens MS, Stukel TA, Swerdlow AJ, Rosso S, Osterlind A, et al. Pregnancy history and incidence of melanoma in women: A pooled analysis. Cancer Causes Control. 2006 Feb;17(1):11–19. http://dx.doi.org/10.1007/s10552-005-0281-y
13. Lea CS, Holly EA, Hartge P, Lee JS, Guerry D 4th, Elder DE, et al. Reproductive risk factors for cutaneous melanoma in women: A case-control study. Am J Epidemiol. 2007 Mar 1;165(5):505–13. http://dx.doi.org/10.1093/aje/kwk040
14. MacKie RM, Bray CA. Hormone replacement therapy after surgery for stage 1 or 2 cutaneous melanoma. Br J Cancer. 2004 Feb 23;90(4):770–2. http://dx.doi.org/10.1038/sj.bjc.6601595
15. Smith MA, Fine JA, Barnhill RL, Berwick M. Hormonal and reproductive influences and risk of melanoma in women. Int J Epidemiol. 1998 Oct;27(5):751–7. http://dx.doi.org/10.1093/ije/27.5.751
16. Paolino G, Panetta C, Cota C, Didona D, Moliterni E, Di Mattia C, et al. Vitamin D receptor immunohistochemistry variability in sun-exposed and non-sun-exposed melanomas. Melanoma Res. 2017 Feb;27(1):17–23. http://dx.doi.org/10.1097/CMR.0000000000000311
17. Paolino G, Bekkenk MW, Didona D, Eibenschutz L, Richetta AG, Cantisani C, et al. Is the prognosis and course of acral melanoma related to site-specific clinicopathological features? Eur Rev Med Pharmacol Sci. 2016 Mar;20(5):842–8.
18. Paolino G, Didona D, Clerico R, DE Vita G, Corsetti P, Ambrifi M, et al. Cancer surveillance series: Role of demographic aspects, altitude and latitude in the extracutaneous malignant melanoma in a residential study. G Ital Dermatol Venereol. 2016 Apr;151(2):133–9.
19. Paolino G, Moliterni E, Didona D, Garelli V, Corsetti P, Lopez T, et al. Clinicopathological features, vitamin D serological levels and prognosis in cutaneous melanoma of shield-sites: An update. Med Oncol. 2015 Jan;32(1):451. http://dx.doi.org/10.1007/s12032-014-0451-4
20. Row D, Weiser MR. Anorectal melanoma. Clin Colon Rectal Surg. 2009 May;22(2):120–6. http://dx.doi.org/10.1055/s-0029-1223844
21. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005 Nov;353(20):2135–47. http://dx.doi.org/10.1056/NEJMoa050092
22. Turri-Zanoni M, Medicina D, Lombardi D, Ungari M, Balzarini P, Rossini C, et al. Sinonasal mucosal melanoma: Molecular profile and therapeutic implications from a series of 32 cases. Head Neck. 2013 Aug;35(8):1066–77. http://dx.doi.org/10.1002/hed.23079
23. Edwards RH, Ward MR, Wu H, Medina CA, Brose MS, Volpe P, et al. Absence of BRAF mutations in UV-protected mucosal melanomas. J Med Genet. 2004 Apr;41(4):270–2. http://dx.doi.org/10.1136/jmg.2003.016667
24. Ascierto PA, Accorona R, Botti G, Farina D, Fossati P, Gatta G, et al. Mucosal melanoma of the head and neck. Crit Rev Oncol Hematol. 2017 Apr;112:136–52. http://dx.doi.org/10.1016/j.critrevonc.2017.01.019
25. Dahlgren L, Schedvins K, Kanter-Lewensohn L, Dalianis T, Ragnarsson-Olding BK. Human papilloma virus (HPV) is rarely detected in malignant melanomas of sun sheltered mucosal membranes. Acta Oncol. 2005;44(7):694–9. http://dx.doi.org/10.1080/02841860500247461

26. Mouawad R, Khayat D, Merle S, Antoine EC, Gil-Delgado M, Soubrane C. Is there any relationship between interleukin-6/interleukin-6 receptor modulation and endogenous interleukin-6 release in metastatic malignant melanoma patients treated by biochemotherapy? Melanoma Res. 1999 Apr;9(2):181–8. http://dx.doi.org/10.1097/00008390-199904000-00011
27. Helmke BM, Deichmann M, Otto HF. Anorectal melanomas do not harbour the Kaposi sarcoma-associated human herpesvirus type 8 DNA. J Med Virol. 2001 May;64(1):47–50. http://dx.doi.org/10.1002/jmv.1016
28. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol. 2006 Sep 10;24(26):4340–6. http://dx.doi.org/10.1200/JCO.2006.06.2984
29. Helmke BM, Mollenhauer J, Herold-Mende C, Benner A, Thome M, Gassler N, et al. BRAF mutations distinguish anorectal from cutaneous melanoma at the molecular level. Gastroenterology. 2004 Dec;127(6):1815–20. http://dx.doi.org/10.1053/j.gastro.2004.08.051
30. Beadling C, Jacobson-Dunlop E, Hodi FS, Le C, Warrick A, Patterson J, et al. KIT gene mutations and copy number in melanoma subtypes. Clin Cancer Res. 2008 Nov 1;14(21):6821–8. http://dx.doi.org/10.1158/1078-0432.CCR-08-0575
31. Antonescu CR, Busam KJ, Francone TD, Wong GC, Guo T, Agaram NP, et al. L576P KIT mutation in anal melanomas correlates with KIT protein expression and is sensitive to specific kinase inhibition. Int J Cancer. 2007 Jul 15;121(2):257–64. http://dx.doi.org/10.1002/ijc.22681
32. Omholt K, Grafström E, Kanter-Lewensohn L, Hansson J, Ragnarsson-Olding BK. KIT pathway alterations in mucosal melanomas of the vulva and other sites. Clin Cancer Res. 2011 Jun 15;17(12):3933–42. http://dx.doi.org/10.1158/1078-0432.CCR-10-2917
33. Kong Y, Si L, Zhu Y, Xu X, Corless CL, Flaherty KT, et al. Large-scale analysis of KIT aberrations in Chinese patients with melanoma. Clin Cancer Res. 2011 Apr 1;17(7):1684–91. http://dx.doi.org/10.1158/1078-0432.CCR-10-2346
34. Satzger I, Schaefer T, Kuettler U, Broecker V, Voelker B, Ostertag H, et al. Analysis of c-KIT expression and KIT gene mutation in human mucosal melanomas. Br J Cancer. 2008 Dec 16;99(12):2065–9. http://dx.doi.org/10.1038/sj.bjc.6604791
35. Hodi FS, Friedlander P, Corless CL, Heinrich MC, Mac Rae S, Kruse A, et al. Major response to imatinib mesylate in KIT-mutated melanoma. J Clin Oncol. 2008 Apr 20;26(12):2046–51. http://dx.doi.org/10.1200/JCO.2007.14.0707
36. Lutzky J, Bauer J, Bastian BC. Dose-dependent, complete response to imatinib of a metastatic mucosal melanoma with a K642E KIT mutation. Pigment Cell Melanoma Res. 2008 Aug;21(4):492–3. http://dx.doi.org/10.1111/j.1755-148X.2008.00475.x
37. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003 Dec 1;21(23):4342–9. http://dx.doi.org/10.1200/JCO.2003.04.190
38. Jiveskog S, Ragnarsson-Olding B, Platz A, Ringborg U. N-ras mutations are common in melanomas from sun-exposed skin of humans but rare in mucosal membranes or unexposed skin. J Invest Dermatol. 1998 Nov;111(5):757–61. http://dx.doi.org/10.1046/j.1523-1747.1998.00376.x
39. Heppt MV, Roesch A, Weide B, Gutzmer R, Meier F, Loquai C, et al. Prognostic factors and treatment outcomes in 444 patients with mucosal melanoma. Eur J Cancer. 2017 Aug;81:36–44. http://dx.doi.org/10.1016/j.ejca.2017.05.014
40. McBrearty A, Porter D, McCallion K . Anal melanoma: A general surgical experience. J Clin Case Rep. 2015;5:493.
41. Van Schaik P, Ernst M, Meijer H, Bosscha K. Melanoma of the rectum: A rare entity. World J Gastroenterol. 2008 Mar 14;14(10): 1633–1635. http://dx.doi.org/10.3748/wjg.14.1633
42. Khan M, Bucher N, Elhassan A, Barbaryan A, Ali AM, Hussain N, et al. Primary anorectal melanoma. Case Rep Oncol. 2014 Jan–Apr;7(1):164–70. http://dx.doi.org/10.1159/000360814
43. Mihajlovic M, Vlajkovic S, Jovanovic P, Stefanovic V. Primary mucosal melanomas: A comprehensive review. Int J Clin Exp Pathol. 2012;5(8):739–53. http://dx.doi.org/10.1309/DVWLTV8FFKC3L80H
44. Chute DJ, Cousar JB, Mills SE. Anorectal malignant melanoma: Morphologic and immunohistochemical features. Am J Clin Pathol. 2006 Jul;126(1):93–100.
45. Bello DM, Smyth E, Perez D, Khan S, Temple LK, Ariyan CE, et al. Anal versus rectal melanoma: Does site of origin predict outcome? Dis Colon Rectum. 2013 Feb;56(2):150–7. http://dx.doi.org/10.1097/DCR.0b013e31827901dd

46. Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. J Am Acad Dermatol. 2007 May;56(5):828–34. http://dx.doi.org/10.1016/j.jaad.2006.06.017
47. Wanebo HJ, Woodruff JM, Farr GH. Anorectal melanoma. Cancer. 1981 Apr 1;47(7):1891–900. http://dx.doi.org/10.1002/1097-0142(19810401)47:7%3C1891::AID-CNCR2820470730%3E3.0.CO;2-K
48. Goldman S, Glimelius B, Pahlman L. Anorectal malignant melanoma in Sweden. Report of 49 patients. Dis Colon Rectum. 1990 Oct;33(10):874–7. http://dx.doi.org/10.1007/BF02051925
49. Roumen RM. Anorectal melanoma in The Netherlands: A report of 63 patients. Eur J Surg Oncol. 1996 Dec;22(6):598–601. http://dx.doi.org/10.1016/S0748-7983(96)92346-X
50. Iddings DM, Fleisig AJ, Chen SL, Faries MB, Morton DL. Practice patterns and outcomes for anorectal melanoma in the USA, reviewing three decades of treatment: Is more extensive surgical resection beneficial in all patients? Ann Surg Oncol. 2010 Jan;17(1):40–4. http://dx.doi.org/10.1245/s10434-009-0705-0
51. Talsma K, van Hagen P, Grotenhuis BA, Steyerberg EW, Tilanus HW, van Lanschot JJ, et al. Comparison of the 6th and 7th editions of the UICC-AJCC TNM classification for esophageal cancer. Ann Surg Oncol. 2012 Jul;19(7):2142–8. http://dx.doi.org/10.1245/s10434-012-2218-5
52. Chae WY, Lee JL, Cho D-H, Yu SK, Roh, J, Kim JC. Preliminary suggestion about staging of anorectal malignant melanoma may be used to predict prognosis. Cancer Res Treat. 2016 Jan;48(1):240–9. http://dx.doi.org/10.4143/crt.2014.305
53. Podnos YD, Tsai NC, Smith D, Ellenhorn JD. Factors affecting survival in patients with anal melanoma. Am Surg. 2006 Oct;72(10):917–20.
54. Singer M, Mutch MG. Anal melanoma. Clin Colon Rectal Surg. 2006 May;19(2):78–87. http://dx.doi.org/10.1055/s-2006-942348
55. Falch C, Mueller S, Kirschniak A, Braun M, Koenigsrainer A, Klumpp B. Anorectal malignant melanoma: Curative abdominoperineal resection: patient selection with 18F-FDG-PET/CT. World J Surg Oncol. 2016; 14: 185. http://dx.doi.org/10.1186/s12957-016-0938-x
56. Yeh JJ, Shia J, Hwu WJ, Busam KJ, Paty PB, Guillem JG, et al. The role of abdominoperineal resection as surgical therapy for anorectal melanoma. Ann Surg. 2006 Dec; 244(6):1012–17. http://dx.doi.org/10.1097/01.sla.0000225114.56565.f9
57. Crosby T, Fish R, Coles B, Mason MD. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev. 2000;(2):CD001215. http://dx.doi.org/10.1002/14651858.CD001215
58. Chapman PB, Einhorn LH, Meyers ML, Saxman S, Destro AN, Panageas KS, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol. 1999 Sep;17(9):2745–51. http://dx.doi.org/10.1200/JCO.1999.17.9.2745
59. Singhal NK, Ostwal VS, Shrikhande SV, Saklani A, Arya S, Ramadvar M. Systemic therapy in anorectal melanoma: Does choice of systemic therapy matter? ASCO 2016; Poster 731.
60. Tacastacas JD, Bray J, Cohen YK, Arbesman J, Kim J, Koon HB, et al. Update on primary mucosal melanoma. J Am Acad Dermatol. 2014 Aug;71(2):366–75. http://dx.doi.org/10.1016/j.jaad.2014.03.031
61. Jehangir W, Schlater N, Singh S, Enakuaa S, Islam MA, Sen S, et al. Anorectal melanoma: A case report and an update of a rare malignancy. World J Oncol. 2015;6:308–10.
62. Khalil DN, Carvajal RD. Treatments for noncutaneous melanoma. Hematol Oncol Clin North Am. 2014 Jun;28(3):507–21. http://dx.doi.org/10.1016/j.hoc.2014.02.006
63. Knowles J, Lynch AC, Warrier SK, Henderson M, Herlot AG. A case series of anal melanoma including the results of treatment with imatinib in selected patients. Colorectal Dis. 2016 Sep;18(9):877–82. http://dx.doi.org/10.1111/codi.13209
64. Tan J. Perianal melanoma with BRAF gene mutation in a young Portuguese Roma native. BMJ Case Rep. 2016:pii: bcr2015212772. http://dx.doi.org/10.1136/bcr-2015-212772
65. Tokuhara K, Nakatani K, Tanimura H, Yoshioka K, Kiyohara T, Kon M. A first reported case of metastatic anorectal amelanotic melanoma with a marked response to anti-PD1-antibody nivolumab: A case report. Int J Surg Case Rep. 2017;31:188–92. http://dx.doi.org/10.1016/j.ijscr.2017.01.028
66. Robert C, Long GV, Brady B. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372:320–30. http://dx.doi.org/10.1056/NEJMoa1412082