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Anorectal Melanoma

Rahul Gupta, Nalini Bansal, Houssem Ammar and Jyoti Gupta

Abstract

Malignant melanoma is an aggressive disease. The anorectal region is the most common site of primary gastrointestinal malignant melanoma. Due to its low incidence, the diagnosis is often delayed. The most characteristic clinical feature of this tumor is its brown-black appearance due to the melanin pigment. However, the pigmentation may be absent in up to 20% cases. Timely diagnosis and treatment are crucial for achieving good long-term outcomes. Surgical excision remains the treatment of choice for localized disease. However, the extent of surgery has been a matter of debate. Anorectal melanoma is a highly malignant disease, and more than 50% cases have metastasis at the time of diagnosis. Targeted therapies especially immune check point inhibitors have brought about a paradigm shift in the management of cutaneous melanoma. They are being increasingly used for mucosal melanomas, and their role in anorectal melanoma is being investigated in various clinical trials.

Keywords: malignant melanoma, anus, rectum, mucosal, check point inhibitors

1. Introduction

Anorectal melanoma (AM) is a rare type of anorectal malignancy. It accounts for about 1% of all anal cancers [1]. Due to its rarity, it is often misdiagnosed as hemorrhoids, rectal adenocarcinoma and polyps. Its early diagnosis and treatment are important to improve the prognosis as it is an aggressive disease with high malignant potential. There are no standard guidelines for the diagnosis, staging and treatment of AM. In this chapter, we have discussed the epidemiological, pathogenesis, clinical manifestations, treatment and prognosis of AM.

2. Epidemiology

Mucosal melanoma (MM) accounts for 1–2% of all melanomas with incidence of 2–2.6 cases per million people/year [2]. The most common sites of MM are head and neck followed by anorectal region [3]. AM is the most common type of gastrointestinal melanoma and the third most common type of melanoma [3]. AM accounts for 16.5% cases of mucosal melanomas [4]. The annual incidence rate of AM is 0.259 in males and 0.407 in females according to Surveillance, Epidemiology, and End Results (SEER) analysis and, the incidence has been steadily increasing over the years [5, 6]. However, the exact reasons for rising incidence are poorly understood. The prevalence of AM is 1.6 to 2.3 times higher in females than males and two times higher in Caucasians than African Americans [7, 8].

3. Pathogenesis and genetics

Melanocytes are derived from the neural crest cells. They migrate to the cutis and mucocutaneous junctions during the embryonal life. The chief function of melanocytes is their antioxidant activity, which helps to counteract the free radicals generated by the ultraviolet rays. Additionally, they contribute to the regional immune response [9, 10]. It has been postulated that the malignant transformation of melanocytes occurs due to oxidative stress and/or immunosuppression [9]. Other theories on AM suggest that they may be derived from Schwann cells of autonomic nervous system or the cells of the amine-precursor uptake and decarboxylation (APUD) system of the gastrointestinal tract [11]. Ultraviolet rays play a central role in the development of cutaneous melanoma (CM) unlike mucosal melanoma (MM). Hence, other pathways are involved in the development of MM which are poorly understood.

MM have different mutation profile compared to cutaneous melanomas [12]. BRAF mutations are infrequent, with an increased rate of c-KIT overexpression [13]. The incidence of BRAF, NRAS and c-KIT mutations are 5–16%, 14–18% and 11–15% respectively [14–16]. The mutation profiles of mucosal melanomas indicate that they have potential sensitivity to CDK4/6 and MEK inhibitors [16]. A study by Newell et al. have identified various mutational signatures in mucosal melanomas [16]. They found that mutations for melanoma in facial sites are different from that found in lower body sites. For example, SF3B1 hotspot mutations are common in AM and vulvovaginal melanomas, unlike other sites. Another study by Donizy et al. found that high poly (ADP-ribose) polymerase 1 (PARP-1) expression alone and along with high indoleamine 2,3-dioxygenase 1 (IDO-1) expression in mucosal melanomas was associated with worse overall and disease-specific survival [17]. Some studies have speculated that some viruses such as human papilloma virus (HPV) and human herpes virus (HHV-8) could be involved in the development of primary MM [11]. However, HPV DNA and HHV-8 DNA could not be detected in cases with AM [18, 19].

4. Clinical features

4.1 Clinical signs and symptoms

The clinical features of AM mimic that of benign anorectal disorders leading to delay in diagnosis. The main clinical symptoms include bleeding per rectum, perianal pain, pruritus ani, tenesmus, perianal mass, inguinal mass (**Figure 1**). It is more frequent in females than males (1.7:1). It is most frequently observed in 6th and 7th decade of life [5]. The most important aspect of clinical diagnosis is a careful perianal and per-rectal examination. AM appears as an ulcerated or nodular lesion with an irregular surface showing brown or black pigmentation (**Figure 1**). Moreover, these are vascular lesions which bleed on touching. Frequently, in about 20% cases, the pigmentation may be absent. In small lesions, a high index of suspicion is required for timely diagnosis due its appearance similar to hemorrhoids. Hence, whenever in doubt, incisional or excisional biopsy should be performed for histopathological examination to diagnose AM. Another important clinical finding in cases of AM is the presence of inguinal lymphadenopathy. Inguinal lymph nodal metastases are usually seen in cases of anal melanoma. In cases with inguinal lymphadenopathy, fine needle aspiration and cytological examination for the enlarged lymph nodes can help in making the diagnosis.

Serum markers can aid in the diagnosis of AM. However, they are elevated in advanced cases of melanoma and often used as an adjunct to the other investigations for diagnosis. Lactate dehydrogenase (LDH) is a commonly used marker
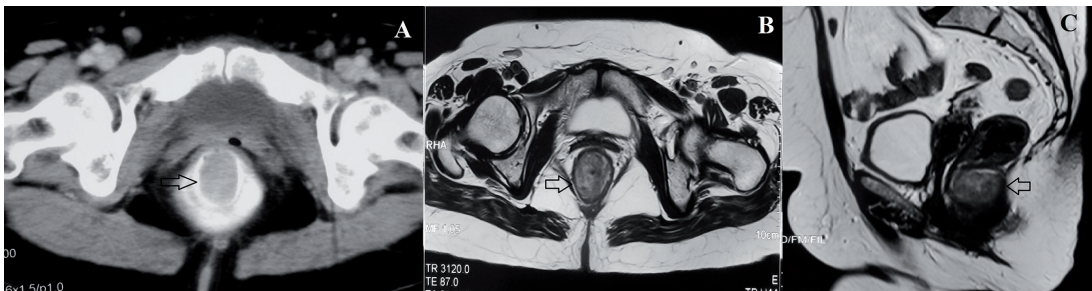
Figure 1.
Perianal examination showing the ulcerated mass in a patient with locally advanced anorectal melanoma.

for the detection of distant metastases in patients with melanoma [20]. Other markers include S-100B, melanoma inhibitor activity (MIA) protein, enolase and YKL-40 [21–24]. Elevated levels of these markers have been associated with a poor prognosis.

4.2 Radiological studies

The main role of radiological investigations is to determine the extent of the disease. Chest radiograph can detect obvious pulmonary metastases while abdominal ultrasound can detect liver metastasis [25]. Computed tomography (CT) is helpful in accurate staging of the disease (**Figure 2**). On CT, the liver lesions show late arterial enhancement and hypoattenuation of liver parenchyma in the portal venous phase [26]. The pulmonary metastases on CT chest appear as multiple end-arterial nodules with tree-in-bud appearance [25]. Magnetic resonance imaging (MRI) is a good imaging modality for accurate assessment of the local invasion of the tumor

Figure 2.
Anorectal melanoma appeared as a heterogeneously enhancing polypoidal mass (arrow) on contrast enhanced CT (A) and MRI (B, C).

as well as for the detection of metastatic lesions in the liver (**Figure 2**) [27]. PETCT is the recommended imaging for the staging and response assessment of metastatic melanoma [20]. Melanoma cells have higher FDG avidity compared to normal tissues due to high metabolic rate [20].

4.3 Endoscopic studies

For deeply located AM, especially rectal melanoma, endoscopy is very useful to visualize the lesions and take biopsies for histological examination. On endoscopy, the lesions appear as black or brownish plaques, ulcers or polyps due to the melanin pigment. The accuracy of endoscopic biopsy ranges from 50 to 100% [28]. The accuracy is low for lesions with atypical endoscopic characteristics. Endoscopic ultrasound is helpful in determining the depth of the lesions especially the extent of anal sphincter involvement and to look for perirectal lymphadenopathy. The lesions appear hypoechoic with uneven internal echoes [28].

5. Histopathology

As none of the clinical features are unique to AM, histological examination of the suspected lesions should be performed for the definitive diagnosis of AM. The main cytological features of AM are highly cellular smear, presence of binucleated or multinucleated cells, and cytoplasmic melanin pigment. However, melanin pigment is found in only about 27% cases [29].

On gross examination, the lesion appears as polypoidal or ulcerated lesion with or without brown-black pigmentation (**Figure 3**). The histological description includes cell type, degree of melanin pigmentation and mitotic index (Ki-67) [20]. Typically, AM consists of spindle-shaped (**Figure 4**) or epitheloid cells with high nuclear pleomorphism and presence of cytoplasmic melanin granules (**Figure 5**) [30]. About 20% cases are truly amelanotic on histology [31]. Four subtypes of AM based on histology are epitheloid, spindle cell, lymphoma-like and pleomorphic [32]. In the absence of melanin pigments, the tumor morphology can mimic lymphoma and gastrointestinal stromal tumors. Immunohistochemistry helps in differentiate AM from other tumors. Melanoma antigens such as S-100, HMB-45 and vimentin are positive in 78, 94 and 100% cases (**Figure 6**) [31]. The characteristic
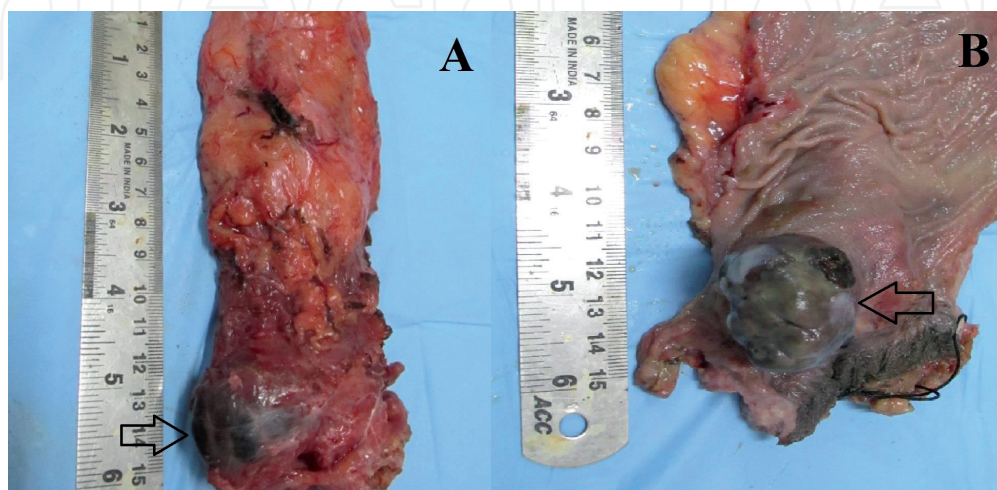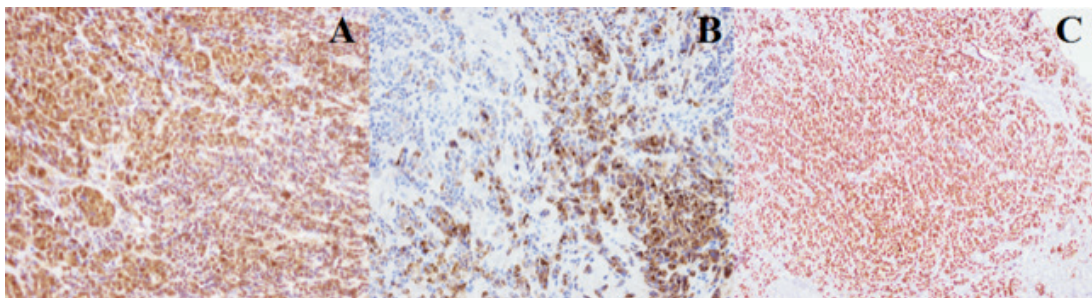

Figure 3.
Gross examination of the specimen after abdominoperineal resection showing the pigmented polypoidal hard growth (arrow) of about 3 cm reaching up to the outer surface (A) and involving the anorectal junction (B).
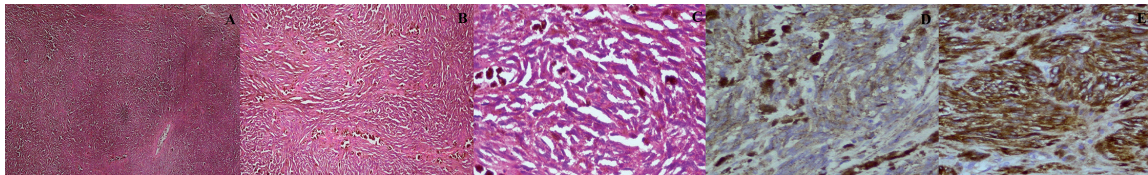
Figure 4.
Histological examination of anorectal melanoma showing the diffuse infiltration of the tissue by spindle-shaped cells with dense eosinophilic cytoplasm and pleomorphic nuclei: (A) H&E x10, (B) H&E x 20, and (C) H&E x 40. Immunohistochemical analysis revealed positive staining with c-KIT (D) and Melan A (E).
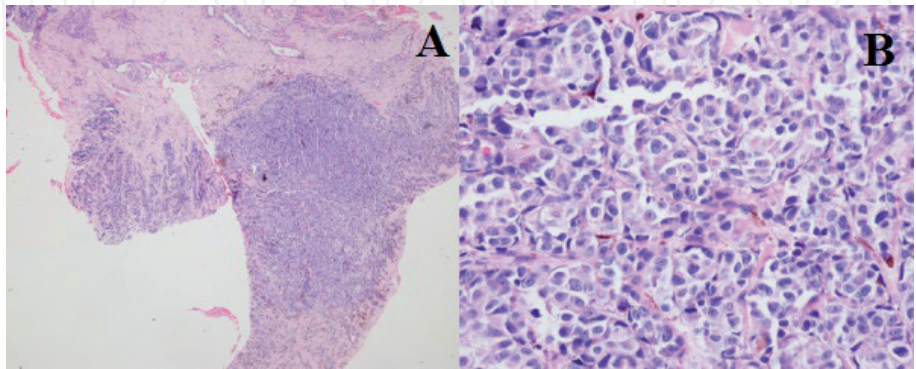
Figure 5.
Microscopic examination of the tumor showing diffuse infiltration of the anorectal region by large epitheloid cells with vesicular and prominent nuclei (A) H&E x 10 and (B) H&E x 40.

Figure 6.
Immunohistochemical analysis of the anorectal melanoma showing positivity for HMB 45 (A), Melan A (B) and SOX 10 (C).

marker of gastrointestinal stromal tumor, c-Kit is positive in about three-fourth cases of AM (**Figure 4**) [32]. In some cases, the tumor cells may show positivity for CEA, CD30 and CD68 similar to colorectal adenocarcinoma and other tumors [33]. Hence, a panel of markers should be tested to confirm the diagnosis of AM in doubtful cases. Some unique markers for melanoma with high specificity and low sensitivity include Melanin A, Mart-1 antibodies [20]. Interestingly, Ki-67 and proliferating cell nuclear antigen (PCNA) immunostains have been found to predict survival in patients with AM [31].

Tumor-infiltrating lymphocytes (TILs) provide a reflection of the tumor microenvironment. Presence of TILs in high concentration is associated with high programmed cell death protein 1 (PD-1) [34]. High PD-1 expression indicates better prognosis for patients with AM due to good response to targeted therapies. TILs can be seen on hematoxylin and eosin stains and also with immunohistochemistry. The majority of these TILs are CD8-positive cells. In a study of 43 AM patients, TILs were present in 55% cases [35].

6. Diagnosis and staging

As CM and MM are known for early hematogenous spread, secondary gastro-intestinal melanomas are not rare. Hence, for differentiation between primary and secondary melanoma, the following criteria must be satisfied: absence of melanoma at any other cutaneous or mucosal sites confirmed by thorough clinical including genital, oropharyngeal, ophthalmological and endoscopic examination; no past history of melanoma and presence of atypical melanocytes in the basal epithelium of the tissue sample [36].

There is no formal staging system for AM. However, the most commonly described system for AM in previous studies is the Ballantye clinical system which has three stages as follows: Stage I – localized disease, Stage II – presence of inguinal or pelvic lymph nodes and stage III – distant metastasis [37–39]. Interestingly, a recent study by Nagarajan et al. involving 160 AM patients found that the clinical American Joint Cancer Committee (AJCC) staging system (8th edition) for CM significantly stratified disease-specific survival of AM patients. Moreover, the authors recommended slight modifications in the AJCC 'T' category criteria of staging for better stratification [40]. Hence, either of the two staging systems can be used to prognosticate the disease in patients with AM.

7. Treatment

The main treatment options for AM are surgery, chemotherapy, radiation therapy and targeted therapies. According to a study which analyzed data of 1333 AM patients from National Cancer Database from 2004 to 2015, the authors found that surgery alone (48.7%) was the most common treatment given to the AM patients [6]. The use of chemotherapy and radiotherapy was similar throughout the study period but there has been a rapid increase in the use of targeted therapies for AM in the last few years. In **Figure** 7, we have provided an overview of the management of patients with AM.

7.1 Surgery

Surgery remains the mainstay of treatment. Most of the previous studies recommend surgical excision for Stage I and II AM. However, the benefit of lymph node
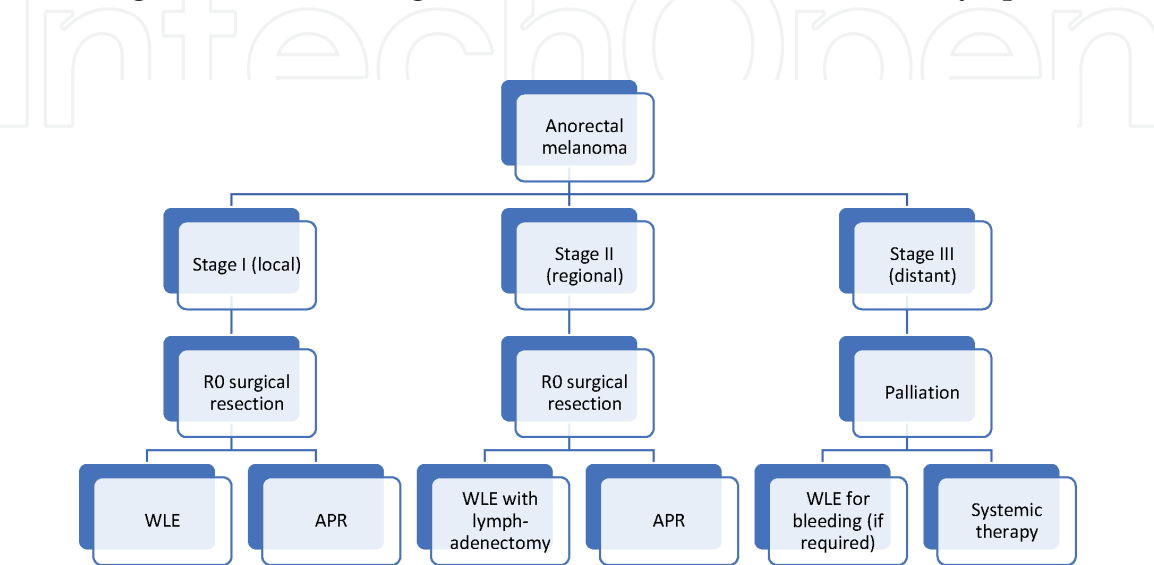
Figure 7.
A suggested algorithm for the management of anorectal melanoma. (WLE—Wide local excision, APR—Abdominoperineal resection, systemic therapy—Chemotherapy, targeted therapies).

dissection in AM has not been established. Unlike rectal adenocarcinoma and CM, lymph nodal metastasis has no significant impact on the long-term survival [41, 42]. The systemic dissemination of the disease occurs early in the course of the disease even before lymph nodal metastasis [43]. The 2020 UK National guidelines recommend R0 surgical resection in the least radical fashion [44]. Lymphadenectomy should be performed in cases with metastatic regional lymph nodes.

The main procedures for AM include: (1) function-preserving procedures such as endoscopic mucosal resection (EMR), wide local excision (WLE); (2) radical procedures such as low anterior resection (LR), abdominoperineal resection (APR). In a meta-analysis of 31 studies [43], 7 studies found APR to be superior to WLE [45–47], 11 studies found WLE to be better than APR [41, 48, 49] while 10 studies reported similar survival outcomes between the two procedures [42, 50, 51]. However, the local recurrence rate was significantly higher in WLE group (57% vs. 21.6%). The most recent study of 305 AM patients treated from 2004 to 2015 found no difference in overall survival (OS) between local and transabdominal resection (2.54 vs. 1.86 years, p = 0.77) [52]. Another recent meta-analysis found no significant difference in OS, disease-free survival (DFS) and local recurrence rates between WLE and APR on analyzing of data from 23, 7 and 19 studies, respectively [53]. So, we believe that WLE with regular surveillance should be the preferred approach. If WLE is not feasible or there is local recurrence without distant metastasis, then APR should be considered [39].

7.2 Chemotherapy

There is no standard chemotherapy regimen for AM due to the rarity of the disease. However, dacarbazine in combination with high-dose interferon and interleukin-2 was found to be effective in 10–20% cases of mucosal melanomas [54]. In a Turkish study of 6 AM patients, all patients received APR followed by adjuvant chemo- and radiotherapy [55]. The adjuvant chemotherapy included dacarbazine and temozolomide. In addition, two patients received ipilimumab, and one patient received interferon therapy. At the mean postoperative follow up of 12.5 months (6–26 months), 4 patients died due to extensive distant metastases while two patients were disease free [55]. In another study of 22 patients with metastatic AM, six patients received dacarbazine while one patient received temozolomide and thalidomide. The median survival in these patients was 9 months [56].

7.3 Radiation therapy

Radiation therapy has been used for palliation or in the adjuvant setting after organ preserving surgery such as wide local excision to reduce the chances of local recurrence. A study by Kelly et al. of 54 patients treated by WLE followed by hypo-fractionated radiotherapy reported good local control in 82% cases but the 5-year OS was only 30% [57].

7.4 Targeted therapies

Immune checkpoint inhibitors have become the standard of care in the treatment of metastatic CM. However, their role in MM is still under investigation. Cytotoxic T-lymphocyte-associated antigen (CTLA-4) and programmed-death (PD1) protein are the most common immune checkpoint targets expressed on activated T-cells with immunosuppressive effects. Ipilimumab is a fully human monoclonal that blocks the binding of CTLA4 with CD80 and CD86 ligands. It was the first agent approved for the treatment of advanced melanoma. It has an indirect

effect on the T-cell mediated antitumor immune response. It prolongs survival in about 20% patients [58].

The ligands of PD1, PDL1 (B7H8) and PDL2 (B7DC) are expressed on tumor cells and other cell types. The immunosuppression of PD1 receptor is due to the interaction between T lymphocytes and tumor cells. PD1 blockage seems to be more effective toward t-cell activation than CTLA-4 inhibition. Nivolumab and pembrolizumab are humanized monoclonal antibodies against PD1. In a study of 44 MM patients having metastasis including 14 patients with AM, pembrolizumab was found to be more effective than ipilimumab in prolonging the PFS [59]. Another study reported the objective response rate of 23% and 37% in MM patients receiving nivolumab alone and in combination with ipilimumab respectively [60]. A study of eight patients treated by immunotherapy, one patient on PD-1 based combination therapy had stable disease and one patient with PD-1 monotherapy had complete response while rest of the six patients had progressive disease [35].

Mitogen-activated protein kinase (MAPK) pathway plays an important role in the cell survival, multiplication and differentiation. Overactivation of this pathway has been detected in various human cancers. Through this pathway many enzymatic kinases are expressed that are part of phosphorylation cascade including RAS, RAK, MEK and ERK kinases [61]. Overactivation of BRAF is one of the most common cause of abnormal MAPK signaling seen in cancers [62]. The MAPK pathway is activated in 40–50% cases of metastatic melanomas [63]. Hence, various BRAF and MEK inhibitors have been used for the treatment of metastatic melanoma.

Dabrafenib is a competitive reversible ATP inhibitor with selective BRAF inhibition. It has been found to be effective in 50–70% cases of melanomas with BRAF V600E or V600K mutations [64, 65]. Additionally, use of MEK inhibitors in combination with BRAF inhibitors such as vemurafenib plus cobimetinib or dabrafenib plus trametinib have prolonged PFS and OS of melanoma patients.

KIT kinase inhibitors such as sorafenib, imatinib, dasatinib, have been found to be very useful in the treatment of gastrointestinal stromal tumors. But they have not been very successful in the treatment of melanomas. However, some studies on KIT-mutated metastatic MM have shown good response to these KIT kinase inhibitors [66–69].

NRAS mutations are present in 15–20% cases of melanoma [70]. Tumors with NRAS mutations have aggressive tumor biology and show poor response to immune check point inhibitors [70]. MEK inhibitors especially binimetinib has shown promising results in phase II/III studies [71]. Several phase I/II trials testing the role of MEK inhibitors in combination with PI3K/AKT inhibitors are underway mainly including metastatic CM patients [70].

In summary, patients with AM, unlike CM, have poor response to targeted therapies. Also, the type of targeted therapy to be used depends upon the mutation analysis of the tumor as highlighted in **Figure 8**. However, the response rates with targeted therapies are better than conventional chemotherapy and are being increasingly used in clinical trials and oncology practice. Some immune checkpoints inhibitors and BRAF inhibitors are being used as adjuvant therapies in the ongoing clinical trials to reduce the recurrence rate after complete surgical excision.

7.5 Other therapies such as immune mediators such as interferon-a, interleukin-2

Studies have found alfa-interferon to improve relapse-free survival and overall survival in patients with CM. In CM, particularly in patients with positive nodal involvement, α-interferon at the dose of 20 MU/m2/day intravenously 5 day weekly
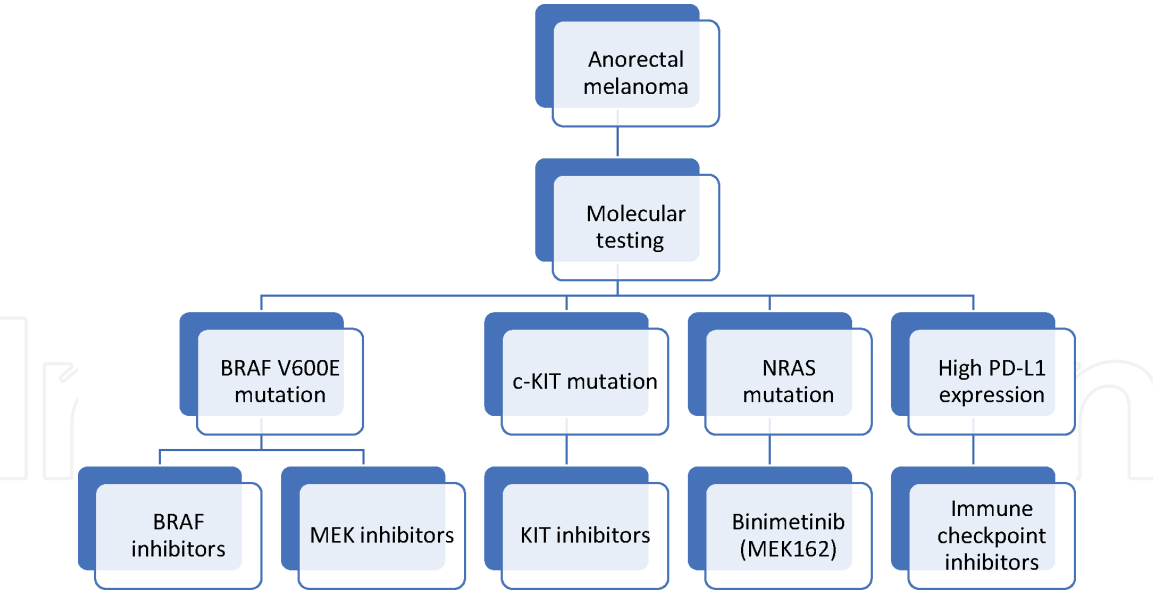
Figure 8.
A flow chart outlining the use of various targeted therapies for the patients with anorectal melanoma (molecular testing—Mutation testing can be done by immunohistochemistry or next-generation or high-throughput sequencing (NSG); BRAF inhibitors—Dabrafenib, vemurafenib, encorafenib; MEK inhibitors—Trametinib, cobimetinib, binimetinib (MEK162); KIT inhibitors—Imatinib, sunitinib, nilotinib; immune checkpoint inhibitors—Ipilimumab, nivolumab, pembrolizumab).

for 4 weeks, followed by 10 MU/m2/day subcutaneously three times weekly for 4–8 weeks had demonstrated a significant prolongation of DFS and OS [72]. However, their role in AM is not clear.

8. Prognostic factors

The 5-year survival rate of colorectal melanoma ranges from 4.3% to 17.4% [73]. The median survival of AM has been reported as 21 months [95% CI: 11–30] [15]. The 5-year OS rates of Stage I, II and III are 26.7%, 9.8% and 0% respectively [35].

A recent study by Menon et al. of 209 nonmetastatic AM patients found no significant difference in the median overall survival with chemotherapy (1.41 vs., 2.24 years, p = 0.16), radiotherapy (2.55 vs. 1.96 years, p = 0.31) and targeted therapy (2.07 vs. 1.96 years, p = 0.95) [52]. This study also found no benefit of adjuvant therapy in nonmetastatic AM cases after surgery. On the other hand, in 116 patients with metastatic disease, targeted therapy showed a trend toward higher survival (1.33 vs. 0.55 years, p = 0.06). On multivariate analysis, younger age, urban location of the patients and surgery were associated with better OS [52]. Other studies have found that age, tumor thickness, presence of ulceration, lymphovascular invasion, perineural invasion and tumor AJCC stage are the main predictors of survival [15, 39, 40].

The reported 1-,2-,3-,4-OS rates have been 67,40,40 and 32% in APR group and 100,100,67, and 67% in WLE group [39]. The median survival in WLE and APR groups were 36 and 13 months respectively [3]. In another study by Bello et al., no significant difference was found between WLE (n = 81) and APR (n = 14) provided the resection margins were tumor-free [74].

The site of origin of melanoma affects the prognosis as seen in cutaneous and mucosal melanoma. Whether the location of the tumor such as anal, rectal or anorectal affects the prognosis is not clear. In a study of 120 AM patients by Bello et al., the authors divided the patients in to three groups: anal (tumor below dentate line), anorectal (tumor at or traversing dentate line) and rectal (tumor above the dentate line). They found no significant difference in the DFS (23 vs. 28 vs. 27 months, p = 0.887) and

OS (22 vs. 28 vs. 27 months, p = 0.696) between the three groups [74]. Additionally, they found no survival benefit with adjuvant radiation or systemic therapy.

In the largest study of 60 Asian patients with AM, the authors found age > 70 years, tumor size more than 5 cm, tumor thickness more than 10.5 mm, lymph nodal metastasis, tumor invasion beyond deep muscular layer to be associated with poor disease-specific survival on univariate analysis. Among these parameters, only age > 70 years and depth of tumor invasion were independent predictors of low disease-specific survival [75].

9. Conclusion

AM is an uncommon malignancy of the anorectal region with high malignant potential. Early diagnosis and treatment are required to achieve good long-term results. Surgical excision remains the mainstay of curative treatment. AM shows poor response to radiotherapy and conventional chemotherapy. Targeted therapies, in the recent years, have shown promising results. Future studies with the use of a combination of chemotherapy, immune check point inhibitors, BRAF inhibitors, and MEK inhibitors are required to improve the long-term survival.

Conflict of interest

The authors have no conflict of interest to declare.

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