Anorectal Melanoma Management Evolution: A Narrative Review

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Richard Sassun[1,†], Tommaso Violante[2,†], Francesco Brucchi[3], Annaclara Sileo[3], Roberto Cirocchi[4], Giulio Mari[1]

[1]Department of Colorectal Surgery, Desio Hospital, ASST Brianza, 20832 Desio, Italy
[2]Alma Mater Studiorum, University of Bologna, 40126 Bologna, Italy
[3]General Surgery Residency Program, University of Milan, 20122 Milan, Italy
[4]Department of Medicine and Surgery, University of Perugia, 06123 Perugia, Italy

Anorectal melanoma (ARM) is one of the rarest and most aggressive subtypes of melanoma, representing less than 1% of all melanomas and 0.1–0.4% of anorectal malignancies. As a mucosal melanoma arising in sun-shielded sites, ARM exhibits distinct molecular features compared with cutaneous melanoma, including low tumor mutational burden, absent ultraviolet signatures, frequent *KIT* proto-oncogene Receptor Tyrosine Kinase (*KIT*) mutations (15–25%), and lower immunogenicity. These biological differences contribute to its rapid progression, late diagnosis, and poor response to traditional therapies. Patients typically present with nonspecific symptoms such as rectal bleeding, often resulting in advanced disease at diagnosis, with up to 67% harboring regional or distant metastases. Management of ARM has evolved significantly over the past decades. Historically dominated by radical abdominoperineal resection, surgical treatment has shifted toward sphincter-preserving wide local excision when negative margins can be achieved, driven by comparable survival outcomes and superior functional results regarding bowel, urogenital, and psychological quality of life. However, high positive margin rates remain a major limitation of local excision. Systemic therapy has transitioned from largely ineffective cytotoxic chemotherapy to modern immunotherapy. Immune checkpoint inhibitors have become the cornerstone of treatment, while *KIT*-mutated tumors may benefit from tyrosine kinase inhibitors. Emerging evidence supports neoadjuvant immunotherapy to improve resectability and downstage tumors, with selected matched cohorts reporting 3-year overall survival rates up to 71–75% when combined with abdominoperineal resection. Survival gains have been modest and largely confined to specific subgroups. Key challenges include the absence of a dedicated staging system, high local recurrence rates, limited durability of responses in metastatic disease, and an immunologically "cold" tumor microenvironment. Multidisciplinary team approaches are essential for individualized care. Future progress depends on biomarker-driven trials, integration of novel strategies such as Chimeric Antigen Receptor T-Cell (CAR-T) therapy, and stronger international collaborative research to improve outcomes in this challenging malignancy.

Keywords: anorectal melanoma; local excision; abdominoperineal resection; immunotherapy; chemotherapy; radiotherapy

Introduction

Anorectal melanoma (ARM) stands out as one of the rarest and most aggressive forms of melanoma. It develops from melanocytes in the mucosal lining of the anal canal or rectum and makes up less than 1% of all melanomas and roughly 0.1% to 0.4% of anorectal malignancies [1–3]. ARM is a subtype of mucosal melanoma; while data from broader mucosal melanoma cohorts are often extrapolated due to rarity, site-specific differences in biology and prognosis warrant cautious interpretation [4,5]. In contrast to cutaneous melanoma, which ties closely to ultraviolet exposure, ARM occurs in sun-shielded mucosal sites, pointing to very different underlying causes. Over recent decades its incidence has, with estimates around 0.3 to 0.4 cases per million people each year in the United States [6]. This gradual rise likely stems from better awareness among clinicians, advances in pathology, and improved cancer registry data, although we still lack clear evidence for any specific environmental or genetic drivers.

The disease mainly strikes older adults, with a median age at diagnosis between 60 and 70 years, and women are affected slightly more often, with a female-to-male ratio around 1.5:1 [7]. Unlike cutaneous melanoma, which disproportionately hits Caucasians, ARM shows no strong ethnic preference. Patients usually present with vague symptoms that mimic everyday problems like hemorrhoids: rectal bleeding dominates (seen in about 80% of cases), along

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Correspondence to: Richard Sassun, Department of Colorectal Surgery, Desio Hospital, ASST Brianza, 20832 Desio, Italy (e-mail: richardsassun@hotmail.it).
† *These authors contributed equally.*
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with a palpable mass, altered bowel habits, tenesmus, or anal discomfort. Because these signs are so nonspecific, diagnosis often comes late. By the time of presentation up to 67% of patients already have regional lymph node spread or distant metastases, which highlights just how quietly and quickly this tumor advances [8,9].

ARM differs sharply from its cutaneous counterpart (Table 1). It carries a lower tumor mutational burden and almost no ultraviolet-related signatures [10,11]. The most frequent mutations involve *KIT* proto-oncogene Receptor Tyrosine Kinase (*KIT*) in 15–25% of cases, Neuroblastoma Rat Sarcoma (*NRAS*) in about 20%, and B-rapidly accelerated fibrosarcoma (*BRAF*) *V600E* in only 3–5%, far below the 50% seen in skin melanoma [10,12–14]. Alterations in Neurofibromin 1 (*NF1*) and amplifications of Cyclin-dependent kinase 4/6 (*CDK4/6*) or Mouse double minute 2 (*MDM2*) also appear [12]. This genetic makeup helps explain why ARM responds less reliably to targeted drugs and shows reduced immunogenicity overall. From a pathogenesis standpoint the tumor seems to arise from melanocytic hyperplasia in the anal transitional zone, possibly fueled by chronic irritation or, in rare instances, viral influences like Human Papilloma Virus (*HPV*), though solid proof remains limited.

Diagnosis and Staging Challenges

Diagnosing ARM usually starts with endoscopic inspection through anoscopy or colonoscopy, followed by biopsy. Imaging with endoanal ultrasound, magnetic resonance imaging (MRI), or Positron Emission Tomography Computed Tomography (PET-CT) helps map local invasion, nodal status, and distant disease. Pathologically the tumor features atypical melanocytes in epithelioid or spindle shapes, and up to 80% lack visible pigment (amelanotic), which makes recognition tricky [15]. Immunohistochemistry with markers such as S-100 Protein (S-100), Marker of Proliferation Ki-67 (Ki-67), *HMB-45*, Melan-A, and SRY-Box Transcription Factor 10 (*SOX10*) usually confirms the diagnosis [7].

One of the biggest hurdles remains the complete absence of a dedicated AJCC or TNM staging system designed specifically for ARM. Adapting the cutaneous melanoma 8th edition AJCC framework or rectal/anal carcinoma TNM rules often leads to inaccurate prognostic stratification in clinical practice, as these systems do not adequately account for the unique mucosal biology, high rates of occult metastases, and anatomic constraints of the anorectal region [16–18]. Therefore, many centers rely on a basic clinical scheme not supported by AJCC or guidelines: Stage I for localized tumors, Stage II for regional nodes, and Stage III for distant spread [19]. However, this system often misses the true prognosis stratification because of its simplicity. Some recent suggestions propose tweaking the 8th edition cutaneous model for ARM by adding details on thickness and lymphovascular invasion, which appear to improve survival stratification [20].

Historical Perspective

ARM has been recognized as a separate entity since the late 19th century, though early reports frequently lumped it together with sarcomas or other anorectal lesions because of its scarcity and unusual features. Case descriptions from that time stressed its explosive behavior, with swift local growth and early distant spread. Until the 1980s treatment relied almost entirely on aggressive surgery, much like the approach used for rectal adenocarcinoma. Abdominoperineal resection, which removes the rectum, anus, and surrounding tissues along with a permanent colostomy, served as the main procedure. Surgeons believed wide margins and thorough lymph node clearance offered the best chance to halt lymphatic dissemination [21].

Systemic options stayed primitive. Traditional adjuvant chemotherapy (e.g., dacarbazine/temozolomide-based regimens) showed low response rates (0–20%) and failed to improve survival in most series, largely due to the low tumor mutational burden and limited immunogenicity of mucosal subtypes [22–24]. These early approaches were abandoned in favor of immunotherapy as evidence of their limited efficacy accumulated, labeling the tumor as both chemoresistant and radioresistant [25]. Series from those years typically reported median survival below 2 years, framing ARM as virtually incurable and a systemic illness right from the start, relegating treatment to symptom relief rather than any real hope of cure [26].

Evolution of Surgical Treatment

Over time surgical management of ARM has shifted dramatically from radical excision toward more conservative, organ-sparing techniques that aim to preserve function while maintaining reasonable oncologic control. Before the 1980s abdominoperineal resection ruled the field [27]. Then retrospective reviews in the 1980s and 1990s began showing similar overall survival between radical resection and wide local excision when clear (R0) margins could be secured [28,29]. Wide local excision, targeting 1–2 cm margins and sparing the sphincter, emerged as the go-to option for early or localized lesions, especially in the anal canal, because it avoids a permanent stoma and maintains continence [30].

The core rationale for this transition is functional preservation, which has been extensively studied in the rectal cancer literature. Quantitative studies on post-operative outcomes indicate that APR is associated with higher rates of urogenital dysfunction, poorer bowel function, and worse psychological quality of life (QoL) compared with sphincter-sparing approaches [31–33]. The catch lies in achieving those clear margins. Wide local excision suffers from positive margins in 30% to 73% of cases due to the tight anatomy around the sphincter complex, and those posi-

Table 1. Comprehensive molecular and immunohistochemical differences between anorectal and cutaneous melanoma.

Feature/Marker	ARM	Cutaneous melanoma	Key implications
UV radiation signature	Absent (no C>T dominance)	Prominent (C>T transitions at dipyrimidine sites)	Different pathogenesis; explains lack of UV link in ARM
Tumor mutational burden	Low (typically 3–8 mut/Mb)	High (median 10–20+ mut/Mb)	Reduced neoantigen load and lower immunogenicity in ARM → poorer response to immunotherapy
BRAF mutation	Rare (3–9%)	Frequent (40–60%)	*BRAF* inhibitors rarely applicable in ARM; routine testing still recommended
NRAS mutation	10–20%	15–30%	Similar frequency but less dominant driver in ARM
KIT mutation/amplification	Common (15–33% mutations)	Rare (2–8%)	Targeted therapy with imatinib or other TKIs is a valid option in mutated ARM
NF1 mutation	Relatively frequent (~15–20%)	Less common (~5–15%)	Alternative *MAPK* pathway activation; more prominent in ARM
Structural/copy-number variants	Higher burden of chromosomal aberrations and structural variant	Lower structural variant burden	Greater genomic instability in ARM
Tumor microenvironment	Lower CD8+ T-cell infiltration, reduced immune activation, and lower *PD-L1* expression	Higher immune-cell infiltration and immune activation	Explains reduced and less durable responses to checkpoint inhibitors in ARM
Epigenetic changes	Frequent hypermethylation patterns and distinct epigenetic profiles	Variable, less prominent hypermethylation	Contributes to immune evasion and therapeutic resistance in ARM
Amelanotic phenotype	Common (50–80%)	Uncommon (5–10%)	Major diagnostic pitfall
S-100	Positive (sensitivity >90–95%)	Positive (sensitivity >95%)	High-sensitivity screening marker for both; nuclear/cytoplasmic pattern
SOX10	Highly sensitive (88–100%)	Highly sensitive (90–100%)	Excellent nuclear marker; particularly useful in amelanotic or spindle-cell cases
HMB-45	Positive (90%; often focal or weaker in amelanotic tumors)	Positive (56–80%; more uniform in most cases)	Melanocytic differentiation marker; loss of maturation gradient supports malignancy in both
Melan-A	Positive (high sensitivity)	Positive (high sensitivity)	Useful for confirming melanocytic lineage; cytoplasmic staining
c-*KIT* (*CD117*)	Frequently positive, especially in *KIT*-mutated cases	Usually negative or weak	Correlates with *KIT* mutation status; helps guide targeted therapy in ARM
Ki-67	Often elevated (>30–50%)	Variable but generally lower in early-stage lesions	Higher proliferation in ARM correlates with more aggressive biology

UV, ultraviolet; ARM, Anorectal melanoma; *BRAF*, B-rapidly accelerated fibrosarcoma; *NRAS*, Neuroblastoma Rat Sarcoma; *KIT*, *KIT* proto-oncogene Receptor Tyrosine Kinase; TKIs, tyrosine kinase inhibitors; *NF1*, Neurofibromin 1; *MAPK*, mitogen-activated protein kinase; *PD-L1*, Programmed Death Ligand 1; *SOX10*, SRY-Box Transcription Factor 10; *HMB-45*, Human Melanoma Black-45; CD8+ T-cell , Cytotoxic T Lymphocyte; *c-KIT* (*CD117*), c-kit proto-oncogene; Ki-67, Marker of Proliferation Ki-67; S-100, S-100 Protein.

tive margins drive high local recurrence rates (up to 67%) along with worse survival [24]. Oncologic risks of WLE may outweigh functional benefits in cases with larger tumors, sphincter involvement, or if positive margins are anticipated; in such scenarios, neoadjuvant therapy or APR should be considered. Large database studies generally find no overall survival edge for radical over local resection across stages, although radical surgery may help in truly localized disease.

However, neoadjuvant strategies are now changing again the conversation. In a matched analysis of 52 patients, neoadjuvant immunotherapy cut positive margins sharply in radical cases (9% versus 55%) but showed no effect in local excisions [34]. Another matched cohort of 96 patients reported 71% 3-year overall survival when neoadjuvant immunotherapy paired with radical surgery, clearly outperforming adjuvant treatments [35]. These results suggest immunotherapy can downstage tumors and improve resectability, possibly bringing radical surgery back into fa-

vor for carefully selected patients; however, these impressive figures derive from specific matched cohorts and may not yet be replicable in broader, unselected populations.

The importance of the multidisciplinary team model cannot be overstated in coordinating advanced imaging, specialized surgery, and evolving systemic therapies. Integrated multidisciplinary team pathways facilitate individualized decision-making, balancing oncologic control with quality of life (QoL), and are increasingly recognized as key to optimizing outcomes in rare aggressive diseases like ARM [36,37].

Evolution of Medical Treatment

Medical approaches to ARM have moved from largely useless cytotoxic drugs to more targeted and immune-based therapies, though results still lag behind those in cutaneous melanoma. Classic chemotherapies like dacarbazine or cisplatin-based regimens produced response rates of only 0–20% with no real impact on survival, so they fell out of favor [22–24].

Various mechanisms of resistance are known nowadays: the primary cytotoxic lesion produced by both dacarbazine and temozolomide is O^6-methylguanine (*O^6-MeG*), which mispairs with thymine during replication and triggers apoptosis via the mismatch repair (*MMR*) pathway. The DNA repair enzyme O^6-methylguanine-DNA methyltransferase (*MGMT*) directly removes this alkyl adduct, completely neutralizing the drug's cytotoxic effect [38,39]. In melanoma cell lines, *MGMT* activity correlates significantly with temozolomide resistance, and *MGMT* transfection directly attenuates the apoptotic response [39,40]. Furthermore, temozolomide itself actively upregulates *MGMT* transcription through extracellular signal-regulated kinases (*ERK*) pathway activation, creating a self-reinforcing resistance loop [41].

In melanoma cells, acquired downregulation of *MMR* proteins (*MutS homolog 2* [*MSH2*], *MutS homolog 6* [*MSH6*], *MutL homolog 1* [*MLH1*]) by 30–80% confers profound resistance to alkylating agents by preventing the recognition of drug-induced DNA damage [42]. This is particularly relevant because ARM shows mutational signatures associated with DNA *MMR* and microsatellite instability, suggesting inherent alterations in this pathway [10].

Moreover, ARM shows absent or mild tumor-infiltrating lymphocytes in 75% of cases. with epigenetic hypermethylation patterns potentially contributing to immune evasion and distinct clinical behavior [11,43,44]. This immunologically "cold" microenvironment means that any immunogenic cell death induced by chemotherapy (which could theoretically amplify the antitumor response) is unlikely to be leveraged effectively.

Single-cell sequencing studies further highlight heterogeneity in immune infiltration and microbiome interactions that may influence immunotherapy response, identifying an antigen-presenting subtype linked to favorable outcomes and a proliferative subtype associated with recurrence, highlighting actionable targets in macrophages [45,46]. An ongoing prospective study profiling gut and mucosal surface microbiomes in mucosal melanoma patients found that microbial signatures correlate with primary tumor site, with distinct bacterial taxa identified in Immune Checkpoint Inhibitors responders (*Streptococcus*, *Collinsella*, *Blautia*) versus non-responders (*Butyricicoccus*) [10].

Radiation, long considered ineffective, now plays an emerging role in local control after surgery. In a series from MD Anderson Cancer Center, hypofractionated schedules (25–36 Gy in 5–6 fractions) after wide local excision deliver 82–88% local and lymph node control with manageable side effects [29], while its use in the metastatic setting only palliate local symptoms like bleeding [47].

However, the real game-changer has been immunotherapy. Immune checkpoint inhibitors such as anti Programmed Death-1 (PD-1) agents (nivolumab, pembrolizumab) and anti Cytotoxic T-Lymphocyte Antigen 4 (*CTLA-4*) such as ipilimumab, achieve objective responses as seen in a series 86 patients with mucosal melanoma receiving nivolumab, ipilimumab, or combination therapy. In particular, the objective response rates were 53% and 60% for nivolumab and combination therapy, respectively [48]. For the subset with *KIT* mutations (around 15–25%), imatinib represents a valid option, reaching roughly 50% in response rates, with improved survival time [49,50]. However, acquired resistance to tyrosine kinase inhibitors frequently develops (often through secondary *KIT* mutations), *NRAS* and *NF1* co-mutations, which activate the pathway downstream of *KIT*, rendering *KIT* inhibition irrelevant. Lastly, *BRAF* mutations are too rare to make *BRAF/MEK* inhibitors a broad option.

Combining modalities matters most. Surgery followed by adjuvant immunotherapy or radiation improves results in localized disease. National Cancer Database trends show chemotherapy dropping while immunotherapy climbs, tied to small but noticeable gains in overall survival [51,52]. Neoadjuvant immunotherapy follows the pattern seen in broader melanoma. Trials such as NADINA and SWOG S1801 highlight how preoperative immunotherapy primes a strong immune response [53,54]. Real-world data from NEO-MEL confirm major responses in 42% and longer relapse-free survival [55]. For ARM neoadjuvant use is still early, but results are promising [35,52,56].

Survival Over Time

In the 1970s population-based SEER data showed 1-year survival around 38%, falling to 10% at 2 years, and median survival of just 17 and 6 months for patients undergoing surgery or not, respectively [57]. The outlook for patients with anorectal melanoma remained grim in the 2000s, with 5-year overall survival and disease-free survival usually below 30% and median survival between 20 and 45

months [58,59]. Aggressive tumor biology, difficulties in obtaining complete resection, and modest responses to most treatments explain this persistently poor picture. This dismal survival has stayed remarkably stable across decades despite the modern diagnostic tools (e.g., improved endoscopy and imaging) and the multiple treatment changes mentioned before which should contribute to faster diagnosis and better outcomes.

The move toward sphincter-sparing local excision took hold in the mid-2000s and 2010s based on retrospective data showing comparable survival with negative margins, yet population analyses found no real era-to-era improvement. Treatment patterns shifted away from routine radical procedures toward local excision and away from chemotherapy, but these adjustments brought no clear population-level survival lift. The tumor's inherent aggressiveness, high rates of nodal or distant involvement at diagnosis (60–70%), and absence of effective drugs kept any progress minimal. Institutional reports from the period commonly described median survival of 15–22 months and 5-year overall survival under 20%, with disease-specific mortality exceeding 65–70% [60].

In the more recent period, roughly from the 2010s forward and especially after immunotherapy approvals around 2011, some encouraging signals have appeared, although gains remain modest and far from universal. NCDB reviews covering 2011–2020 or 2021 document immunotherapy uptake rising sharply alongside declining chemotherapy [51]. Median overall survival in later cohorts inches up slightly in select analyses, with stage-specific benefits: for stage III/IV disease treated with immunotherapy median survival roughly doubles in certain subgroups (from 6.7 months to 13.3 months for stage IV disease, from 20.3 to 27.2 months for stage III disease) [22,61]. Recent studies revealed that neoadjuvant immunotherapy paired with radical surgery delivers standout 3-year overall survival of 71–75% in matched groups, well above historical adjuvant chemotherapy figures of 8–45% [35,52]. Still, these advantages seem limited to patients who can tolerate radical resection with clear margins.

Treatment Options in Metastatic Disease

Once anorectal melanoma becomes metastatic the situation turns especially bleak, with median overall survival falling below 12 months and few treatments offering lasting benefit. Because dedicated trials remain scarce due to rarity, management draws heavily from mucosal melanoma experience. Immune checkpoint inhibitors serve as the primary option. Single-agent anti-PD-1 therapy produces modest objective responses, while combinations push responses toward 40%, though durability stays shorter than in cutaneous disease [48]. For *KIT*-mutated tumors imatinib provides brief responses before resistance sets in [49]. Chemotherapy serves mainly palliative purposes with low activity, while palliative radiation helps control local symptoms like bleeding, and in oligometastatic settings metastasectomy sometimes enters consideration [47,54,62]. However, these treatments need further investigation, as their role in ARM is still underexplored.

Remarkably, even in this resistant setting, isolated cases of complete response emerge and offer hope. One patient with rectal mucosal melanoma achieved durable complete response after neoadjuvant ipilimumab plus nivolumab, allowing sphincter preservation and remaining relapse-free at 2 years [63]. This exceptional outcome hints that certain biomarkers, perhaps high tumor mutational burden or strong Programmed Death Ligand 1 (*PD-L1*) expression, could identify the rare responders and deserve closer investigation.

Conclusions

Anorectal melanoma remains a rare and highly aggressive tumor with management that continues to evolve. We have moved from an era of routine radical surgery to a palliative surgery to a more multimodal strategy that increasingly incorporate neoadjuvant immunotherapy. Progress seems promising, particularly in selected patients who achieve clear margins after preoperative treatment, yet major obstacles persist around accurate staging, effective options for metastatic disease, and reliable constant tumor responses. Progress seems promising, particularly in selected patients who achieve clear margins after preoperative treatment, yet major obstacles persist around accurate staging, effective options for metastatic disease, and reliable tumor responses across unselected populations. Future trials should explore combinations with radiotherapy, targeted agents, and novel modalities such as Chimeric Antigen Receptor T-Cell (CAR-T) therapy. Biomarker-guided trials and innovative medical-surgical combinations will be crucial to finally improve the trajectory of this challenging disease, while updated international guidelines will further strengthen evidence-based practice.

Availability of Data and Materials

Not applicable.

Author Contributions

RS and TV conceptualized the review and drafted the manuscript. FB and RC performed the data analysis. GM conceived and designed the study. AS conducted the literature search and methodology implementation. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Roberto Cirocchi is serving as one of the Editorial Board and Guest Editor members of this journal. Giulio Mari is serving as one of the Guest Editor members of this journal. We declare that Roberto Cirocchi and Giulio Mari had no involvement in the peer review of this article and have no access to information regarding its peer review. Other authors declare no conflict of interest.

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