ORIGINAL CONTRIBUTION

Approaches to Surgical Management of Anorectal Melanoma in the Pre- and Post-Immunotherapy Eras

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BACKGROUND: Although revolutionary in cutaneous melanoma, immune checkpoint inhibitors have shown reduced efficacy in anorectal melanoma. Nevertheless, their emergence and the possibility of improved outcomes may have changed the surgical management paradigm.

OBJECTIVE: To review the surgical management of anorectal melanoma in pre- and postimmunotherapy eras.

DESIGN: A retrospective cohort study from the Melanoma Institute Australia Research Database.

SETTINGS: A quaternary melanoma referral center.

PATIENTS: Patients with anorectal melanoma from 1958 to 2021 were included.

INTERVENTIONS: The use of abdominoperineal resection and wide local excision were compared in pre- and postimmunotherapy eras from the first use in 2014.

MAIN OUTCOME MEASURES: Type of surgery performed over time and overall survival.

RESULTS: A total of 56 patients were identified with anal (57.1%), anorectal (16.1%), and rectal melanoma (26.8%). Initial management was abdominoperineal resection (37.5%), low anterior resection (3.6%), wide local excision (46.4%), and nonsurgical (12.5%) in metastatic or unresectable disease. Immunotherapy and targeted therapies were used in 21 patients (37.5%) from 2014, with no difference in mode of surgical management in pre- and postimmunotherapy eras ($p = 0.134$). Five-year survival was 12.5% for the entire cohort, with no significant difference comparing patients receiving wide local excision or abdominoperineal resection (15.4% vs 14.3%, log rank $p = 0.77$). Involved margins were significantly associated with wide local excision (15.4% vs 4.8%, $p = 0.016$) with similar rates of local recurrence (15.4% vs 14.3%, $p = 0.58$).

LIMITATIONS: The rarity of anorectal melanoma resulted in a small cohort managed over 63 years. Early checkpoint inhibitor trials excluded patients with mucosal melanoma, limiting access in this cohort.

CONCLUSIONS: Despite the introduction of immunotherapy, surgery remains pivotal in the management of anorectal melanoma. Surgical resection may be curative and prevent morbidity due to locoregional progression, but it can come at the cost of reduced quality of life. Centralized management in experienced centers should be encouraged for optimal multidisciplinary management. See **Video Abstract**.

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ENFOQUES EN EL EL TRATAMIENTO QUIRÚRGICO DEL MELANOMA ANO-RECTAL EN LAS EPOCAS PREVIA Y POSTERIOR A LA INMUNOTERAPIA

ANTECEDENTES: Si bien han sido revolucionarios en el tratamiento del melanoma cutáneo, los inhibidores de los puntos de control inmunitario han demostrado reducida eficacia en el tratamiento del melanoma ano-rectal. Sin embargo, su advenimiento y la posibilidad de obtener

mejores resultados podrían haber cambiado el paradigma del tratamiento quirúrgico.

OBJETIVO: Revisar el tratamiento quirúrgico del melanoma ano-rectal en las épocas previa y posterior a la inmunoterapia.

DISEÑO: Estudio retrospectivo de cohortes de la base de datos de investigación del Instituto del Melanoma de Australia (MRD2).

ESCENARIO: Centro de referencia cuaternaria para melanomas.

PACIENTES: Pacientes con melanoma ano-rectal desde 1958 hasta 2021.

INTERVENCIONES: Se comparó la resección abdominoperineal y la excisión local ampliada en las épocas previa y posterior a la inmunoterapia desde su primer uso en 2014.

PRINCIPALES MEDIDAS DE RESULTADOS: Tipo de cirugía realizada a lo largo del tiempo y sobrevida general.

RESULTADOS: Se identificaron 56 pacientes con melanoma anal (57,1%), ano-rectal (16,1%) y rectal (26,8%). El tratamiento inicial fue la resección abdominoperineal (37,5%), la resección anterior baja (3,6%), la excisión local amplia (46,4%) y el tratamento no quirúrgico (12,5%) en enfermedad metastásica o irresecable. Se utilizaron inmunoterapia y terapias dirigidas en 21 pacientes (37,5%) a partir de 2014 sin diferencias en el modo de tratamiento quirúrgico en las épocas previas y posteriores a la inmunoterapia (p = 0,134). La supervivencia a 5 años fue del 12,5% para toda la cohorte sin diferencias significativas al comparar a los pacientes que recibieron escisión local amplia o resección abdominoperineal (15,4% frente a 14,3%, log rank p = 0,77). Los márgenes afectados se asociaron significativamente con una escisión local amplia (15,4% frente a 4,8% p = 0,016) con tasas similares de recurrencia local (15,4% frente a 14,3% p = 0,58).

LIMITACIONES: El melanoma ano-rectal es poco frecuente, por lo que presentamos una pequeña cohorte tratada a lo largo de ocho décadas. Los primeros ensayos con inhibidores de puntos de control excluyeron a los pacientes con melanoma mucoso, lo que limitó el acceso en esta cohorte.

CONCLUSIONES: A pesar del advenimiento de la inmunoterapia, la cirugía sigue siendo fundamental en el tratamiento del melanoma ano-rectal. La resección quirúrgica puede ser curativa y prevenir la morbilidad debido a la progresión locorregional, pero puede tener el costo de una calidad de vida reducida. Finalmente, debe promoverse el tratamiento centralizado en centros experimentados para un tratamiento multidisciplinario óptimo. *(Traducción—Dr. Xavier Delgadillo)*

KEY WORDS: Anorectal; Immunotherapy; Melanoma; Mucosal; Surgery.

Anorectal melanoma is a rare and aggressive form of mucosal melanoma encountered by colorectal surgeons and surgical oncologists. It represents less than 2% of melanoma presentations and less than 1% of lower GI tumors, with a reported 5-year survival of 12% to 18%.[1] Given the rarity of anorectal melanoma, only limited evidence exists to guide appropriate surgical management of both the primary tumor and draining node field.

Although the emergence of effective immunotherapies has revolutionized the management of cutaneous melanoma, these are less active in mucosal melanoma, highlighting the need for effective multidisciplinary strategies in anorectal melanoma patients.[2] The mechanism of action of immunotherapy may be limited because of significant biological differences between cutaneous and mucosal melanoma, including reduced tumor-infiltrating lymphocytes and programmed death-ligand 1 expression.[3] Reduced efficacy of targeted therapy is reflected in lower rates of NRAS and BRAF mutations (9% and 4% on meta-analysis) and an increased incidence of KIT mutations (8%).[4] KIT-mutated anorectal melanomas are initially susceptible to kinase inhibitors such as imatinib; however, they are known to rapidly mutate and develop resistance.[5] Significant enthusiasm for immunotherapy in anorectal melanoma has been seen in the United States, with 21.27% of patients in the National Cancer Database receiving immunotherapy in 2015 compared with 8% of patients in 2013, whereas overall rates of surgical management have remained largely unchanged.[6]

Abdominoperineal resection (APR) is a radical operative strategy that has been traditionally recommended for improved local control in patients with advanced disease in studies published before the use of immunotherapy.[7] In selected cases, wide local excision (WLE) is an alternate approach that may provide similar overall survival despite an increased incidence of local recurrence.[8] Despite evidence supporting organ preservation with improved quality of life and the absence of a survival benefit, the proportion of patients undergoing APR for anorectal melanoma has remained steady in the United States during the past 30 years.[9] There is significant variation in practice worldwide, with APR being more common overall in publications from Asian and Indian centers and with WLE being used more commonly in US and European centers.[10] Although an advantage of APR is concurrent total mesorectal excision, no significant difference has been shown in disease-specific survival in patients with positive or negative mesorectal lymphadenopathy.[11] The role of lymphadenectomy, while advantageous in gaining local control, remains unclear in promoting survival in anorectal melanoma in studies before the introduction of immunotherapy.[12] Furthermore, distal lesions are more

likely to have lymphatic drainage to superficial inguinal lymph nodes, necessitating inguinal or ilioinguinal node dissection in cases where there is evidence of metastasis to these node fields.

This retrospective cohort study aims to examine trends in surgical treatment and survival data of anorectal melanoma in the pre- and postimmunotherapy eras for patients treated at a large quaternary melanoma referral center (Melanoma Institute Australia [MIA]).

MATERIALS AND METHODS

A search for all patients presenting with anorectal melanoma from the MIA MRD2 database was performed. Study design proceeded in line with the Strengthening the Reporting of Observational Studies in Epidemiology statement with ethics approval provided by the MIA research ethics committee.[13] A standardized data extraction form was used by one author (J.A.P.) to code data regarding clinicopathological characteristics, surgical and adjuvant management, recurrence, and overall survival from patient notes, imaging, and histopathology reports. Patients were discussed at the MIA or Sydney Melanoma Unit multidisciplinary team meeting from the 1980s with a personalized approach to treatment determined by expert consensus. Staging was performed with CT of the chest, abdomen, and pelvis and/or FDG–PET CT on all patients in the modern era (n = 32). APR was offered to patients with evidence of mesorectal node involvement identified on radiological staging. Tumors were classified as anal, anorectal, or rectal based on position relative to the dentate line on clinical examination or endoscopy by the referring surgeon as well as histopathology. A simplified staging system for anorectal melanoma was used as described by Ballantyne, with stages I, II, and III corresponding to local disease and regional and distant metastases, respectively.[14] The pre- and postimmunotherapy eras were determined by the first use of immunotherapy in our cohort of anorectal melanoma patients in 2014. Adjuvant checkpoint inhibitor immunotherapy was considered for all patients with node-positive or metastatic disease. Sentinel lymph node biopsy was performed concurrently with definitive surgery from 2003 and only considered for distal lesions where the spread to the inguinal lymph node basin was considered likely in the absence of clinically evident lymphadenopathy.

Descriptive statistics were performed to characterize tumor and patient demographics as well as management. Univariate analysis was performed using the Student *t* test to investigate differences in clinicopathological characteristics between patients who received WLE or APR as initial surgery. A p value of <0.05 was considered significant. Kaplan-Meier curves were generated and log-rank analysis was performed to determine overall survival from the date of initial diagnosis and compare those who received WLE or APR. Survival was censored at 5 years. Analyses were performed with IBM SPSS version 29.0.

RESULTS

A search of the MIA MRD2 database identified 56 patients with anorectal melanoma spanning presentation and treatment from 1958 to 2021. Thirty patients were men (53.6%) with a mean age of 62.16 years (SD 12.74) at diagnosis (Table 1). Primary melanoma was classified as anal (n = 32), anorectal (n = 9), or rectal (n = 15) in relation to the histological transition of squamous to columnar epithelium. The mean tumor thickness was 10.7 mm (SD 7.98).

The surgical management of the primary melanoma and any subsequent operations are summarized in Figure 1. WLE was performed for 21 patients with anal melanomas (65.6%), of whom 4 had involved margins. Two of these patients subsequently underwent APR and 1 patient refused further surgery. An additional 2 patients returned for repeat WLE for local recurrence. Three of 9 patients (33.3%) with anorectal melanoma underwent WLE. Two of these patients also subsequently required an APR: 1 for involved margins and 1 for local recurrence. The most common initial management of rectal melanoma was APR (46.7%; n = 7), with 2 patients managed by low anterior resection (LAR). There was no perioperative 30-day mortality associated with patients managed surgically.

Overall, 23 patients (41.1%) had clinically detected lymphadenopathy at initial staging. Sentinel lymph node biopsies were performed in 50% of patients (n = 5/10) with clinically node-negative anal melanoma at the time of definitive WLE after 2003. The nodes of all 5 patients localized to superficial inguinal nodes, with positive nodes identified in 2 patients. One patient progressed to completion of inguinal lymphadenectomy, whereas the other refused further management. Mesorectal nodes were involved in 70% of patients (n = 16) who underwent upfront APR or LAR for all primary locations. Four of 5 patients (80.0%) who progressed to APR after WLE also had positive mesorectal nodes on histopathology.

Eleven patients (19.6%) had distant metastatic disease at presentation. Seven of these patients did not undergo surgical resection, 3 were treated with checkpoint inhibition immunotherapy, 2 dacarbazine chemotherapy, and 2 did not receive any treatment. A defunctioning colostomy was performed for 2 patients receiving systemic therapy.

Immunotherapy and targeted therapies were administered to 21 patients (37.5%) in the entire cohort from 2014. Fourteen patients (67%) had node-positive or distant disease at presentation, whereas the remainder received subsequent systemic therapy for disease progression or recurrence. Seven patients (33.3%) received PD-1 inhibitors (nivolumab or pembrolizumab) as monotherapy,

TABLE 1. Clinicopathological features comparing initial surgical management modality for all patients with anorectal melanoma

Characteristic	*APR (N = 21), n (%)*	*LAR (N = 2), n (%)*	*WLE (N = 26), n (%)*	*Nonsurgical (N = 7), n (%)*	*p*[a]
Age, y	61.73 ± 11.58	68.14 ± 11.29	60.43 ± 13.26	70.43 ± 13.88	0.092
Sex					0.310
Male	13 (61.9)	1 (50.0)	12 (46.2)	4 (57.1)	
Female	8 (38.1)	1 (50.0)	14 (53.8)	3 (42.9)	
Year of presentation					0.134
2014–2021 (postimmunotherapy)	8 (38.1)	1 (50.0)	7 (26.9)	3 (42.9)	
1958–2013 (preimmunotherapy)	13 (61.9)	1 (50.0)	19 (73.1)	4 (57.1)	
Location					0.024[b]
Anal	8 (38.1)	0 (0.0)	21 (80.8)	3 (42.9)	
Anorectal	6 (28.6)	0 (0.0)	3 (11.5)	0 (0.0)	
Rectal	7 (33.3)	2 (100.0)	2 (7.7)	4 (57.1)	
Melanoma thickness, mm	8.54 ± 5.061	33.50 ± 12.02	9.69 ± 6.034	16.50 ± 12.02	0.846
Ulceration	18 (85.7)	2 (100.0)	18 (69.2)	4 (57.1)	0.377
Node involvement location					NA
Inguinal	0 (0.0)	0 (0.0)	4 (15.4)		
Mesorectal	15 (71.4)	1 (50.0)	0 (0.0)		
Involved margins	1 (4.8)	0 (0.0)	4 (15.4)		0.016[b]
Initial stage					0.002[b]
I (local)	6 (28.6)	1 (50.0)	15 (57.7)	0 (0.0)	
II (regional metastasis)	12 (57.1)	0 (0.0)	5 (19.2)	0 (0.0)	
III (distant metastasis)	2 (9.5)	1 (50.0)	1 (3.8)	7 (100)	
Molecular testing					NA
BRAF	0 (0.0)	1 (50.0)	2 (7.7)	0 (0.0)	
NRAS	1 (3.8)	0 (0.0)	1 (3.8)	1 (14.3)	
KIT	0 (0.0)	1 (50.0)	1 (3.8)	0 (0.0)	
Not performed	9 (42.9)	0 (0.0)	18 (69.2)	3 (42.9)	
Checkpoint inhibitor	10 (47.6)	1 (50.0)	5 (19.2)	3 (42.9)	0.001[b]
Targeted therapy	1 (4.8)	0 (0.0)	1 (3.8)	0 (0.0)	0.764
Radiotherapy					NA
Adjuvant	3 (14.3)	0 (0.0)	2 (7.7)	0 (0.0)	
Primary treatment	0 (0.0)	0 (0.0)	0 (0.0)	2 (29.1)	
Treat local recurrence	0 (0.0)	0 (0.0)	1 (3.85)	0 (0.0)	
Recurrence					
Local	3 (14.3)	2 (100.0)	4 (15.4)	0 (0.0)	0.583
Regional	5 (23.8)	1 (50.0)	6 (23.1)	1 (14.3)	0.909
Distant	12 (57.1)	2 (100.0)	11 (42.3)	4 (57.1)	0.942

APR = abdominoperineal resection; LAR = low anterior resection; NA = not applicable (test not performed); WLE = wide local excision.
[a]Student *t* test comparing APR with WLE.
[b]Significant *p* value.

whereas 4 patients (19.0%) were treated with the cytotoxic T-lymphocyte–associated protein 4 inhibitor ipilimumab. Eight patients (38.1%) received combination anti–PD-1 and anti–cytotoxic T-lymphocyte–associated protein 4 immunotherapy. Two patients received targeted therapies in 2018 and 2021, respectively, including 1 patient with a BRAF V600E mutation who received a combination of dabrafenib and trametinib and another who received sorafenib. Molecular testing was performed on 26 patients after commencement in 2008. From this group, 3 patients (11.5%) were diagnosed with BRAF, 3 (11.5%) NRAS, and 2 (7.7%) KIT mutations. Before 2014, a small proportion of patients received dacarbazine chemotherapy for metastatic disease (n = 6; 10.7%). There was no significant difference in the modality of surgical management of the primary tumor (WLE vs APR) after the introduction of immunotherapy in our cohort in 2014 ($p = 0.134$).

Eight patients (14.3%) received radiotherapy locally to the anorectum or pelvis. This was delivered as adjuvant therapy to the regional lymph node basins after resection in 5 patients, local recurrence in 1 patient, and as definitive treatment of the primary melanoma in 2 patients.

Distant recurrence occurred frequently in all treatment groups (Table 1). The most common sites of distant metastases were to the liver (n = 16; 55.2%), then the lung (n = 10; 34.5%) and retroperitoneum (n = 6; 20.7%). Regional recurrence occurred most frequently in inguinal nodes (n = 9; 69.2%), then pelvic nodes (n = 3; 23.1%), with a single patient developing both inguinal and pelvic recurrence. Five-year overall survival for the entire cohort was 12.5% with no significant difference for patients receiving WLE or APR (15.4% vs 14.3%, log rank $p = 0.77$; Fig. 2). Five-year recurrence-free survival was not significantly different comparing APR and WLE in our series (11.5%

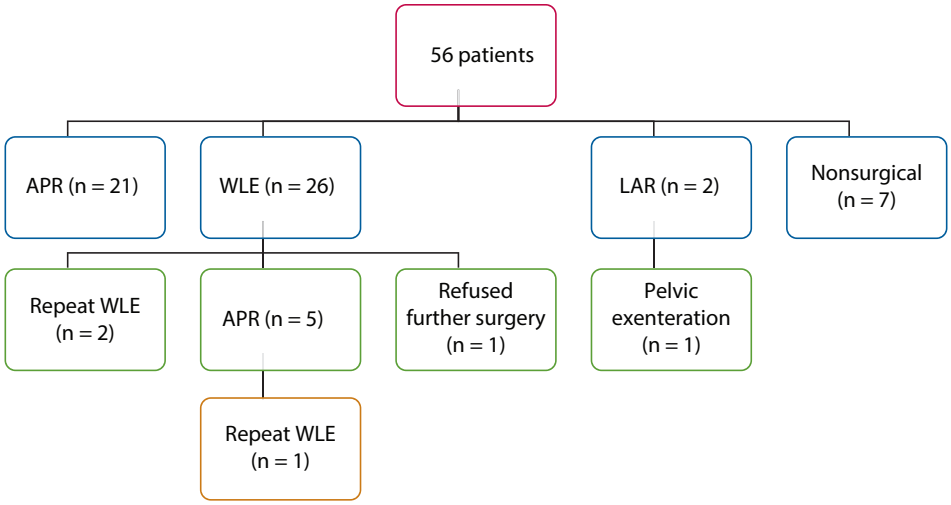

FIGURE 1. Flow chart of surgical management of an entire cohort of patients with anorectal melanoma. APR = abdominoperineal resection; LAR = low anterior resection; WLE = wide local excision.

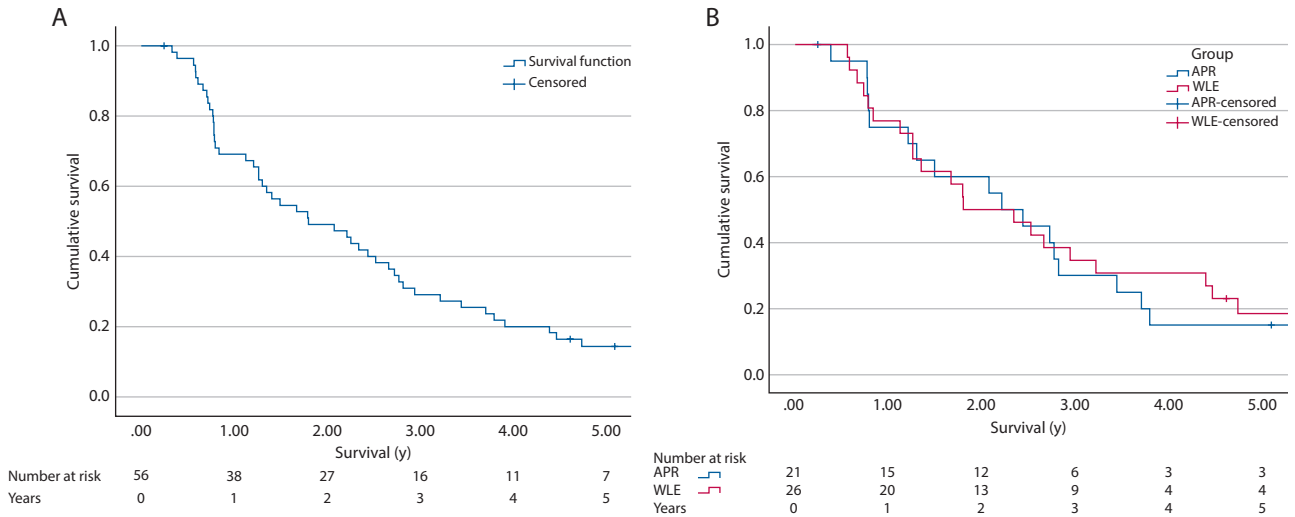

FIGURE 2. Kaplan-Meier graph demonstrating all-cause 5-y mortality for (A) the entire cohort of 56 patients with anorectal melanoma and (B) subgroup analysis of survival comparing WLE with APR (log rank $p = 0.77$). APR = abdominoperineal resection; WLE = wide local excision.

vs 4.8%, log rank $p = 0.278$). The mean time of follow-up was 2.88 years.

DISCUSSION

This study documents the experience of a single institution with anorectal melanoma since 1958. Consistent with previous studies, our cohort demonstrated poor overall survival and high rates of distant metastasis regardless of treatment modality.[9]

Our series demonstrates the role of both WLE and APR in the management of anorectal melanoma. Although distance from the anal verge is an important determinant of surgical decision-making in colorectal cancer, previous comparisons of APR and WLE in anorectal melanoma do not account for this.[9] WLE was performed mostly for anal and anorectal melanomas (92.3%) in our series, suggesting that access to tumors above the anal verge influenced surgical decision-making. Transanal resection techniques have been in a developmental phase during the course of this study and are certainly not ubiquitously available. One rectal melanoma was completely excised by WLE using transanal minimally invasive surgery by a specialist colorectal surgeon, highlighting the potential role of transanal minimally invasive surgery (or equivalent) in the treatment of anorectal melanoma for WLE of tumors located in the proximal two-thirds of the rectum.[15] This patient subsequently had a local recurrence but survived >5 years with the administration of nivolumab. Two LARs were also performed for rectal melanomas, both of which resulted in local recurrences. No studies exist comparing LAR to

APR as an alternative treatment for rectal melanoma. The purported advantages of WLE are maintenance of bowel continuity and sphincter function, lower perioperative morbidity, and improved long-term quality of life.[8] Patients who undergo WLE as the primary surgical modality should be warned of the risk of incomplete excision, with 4 patients (15.2%) in our series requiring a subsequent APR for involved margins. In a Swedish series, 37% of patients (n = 32/86) undergoing WLE had an R2 resection compared with only 11% of patients (n = 7/66) who received APR ($p < 0.001$).[16] In our study, there was no difference in the local recurrence of disease comparing APR and WLE. There was also no significant difference in 5-year overall survival between the 2 approaches.

Considering the absence of survival advantage and similar rates of local recurrence, this study supports the use of WLE over APR as an initial approach for anorectal melanoma where an R0 resection is technically feasible and continence can be maintained except where there is evidence of isolated mesorectal lymphadenectomy. This is also supported by current Australian Cancer Council guidelines as well as British national guidelines, albeit based on low-quality evidence.[17,18] Given the significant risk of local and distant recurrence regardless of approach, a rigorous follow-up schedule for patients after WLE is also advised, including a digital rectal examination every 3 months, palpation of inguinal node basin, and proctoscopy or sigmoidoscopy along with CT of the chest, abdomen, and pelvis every 6 months for the first 3 years. British guidelines also suggest repeat WLE for salvage after R1 resection with APR or systemic therapy used if sphincter complex function cannot be maintained.[18]

Variability in patterns of lymph node metastasis is another consideration in both resection of the primary tumor and management of the draining node field. Position in relation to the dentate line has been shown to have an inconsistent association with inguinal versus mesorectal lymphadenopathy in anorectal melanoma.[11] In our study, positive mesorectal nodes were harvested in the majority of upfront APRs (71.4%) and in salvage APRs after WLE (80.0%) regardless of tumor position. Two of 5 (40%) sentinel lymph node biopsies for anal lesions were positive for metastatic disease. The purportedly higher node positivity rate of more proximal tumors may reflect later diagnosis from less symptomatic disease compared with anal disease or the increased lymph node yield gained in performing APR, although the numbers in each group in our series are too small to draw meaningful conclusions. The use of PET-CT was not universally available in our patient cohort. However, this modality has an established role in the staging and management of patients with cutaneous melanoma and may be of use in determining the optimal surgical approach for individual patients with anorectal melanoma.[19] Patients with node-positive disease have universally poor survival outcomes regardless of whether they undergo lymphadenectomy or not, which likely reflects a more aggressive tumor biology compared to cutaneous disease.[11]

The management and classification of anorectal melanoma have been influenced by studies of cutaneous melanoma despite established evidence of disparate biological behavior and immunogenicity. The use of targeted therapy with BRAF/MEK inhibitors was limited in our cohort due to low rates of BRAF mutations in mucosal melanoma.[4] Checkpoint inhibitors were readily adopted for the management of all patients with stage II and III disease in our cohort from 2014 onward (n = 19), including 5 patients as part of clinical trials. Due to the rarity of anorectal melanoma, studies tend to be nonrandomized, with low patient numbers and variable patient and tumor characteristics. Thus, the efficacy of immunotherapy in anorectal melanoma and which patient subgroups may benefit the most is unclear. A recent Japanese study showed favorable survival outcomes for checkpoint inhibition against dacarbazine (2-year overall survival 61.4% vs 0%, $p = 0.048$) in patients with unresectable or metastatic disease, whereas a recent American study showed no improvement in 5-year survival for patients receiving adjuvant therapy after surgery compared with surgery alone.[2,20] Anorectal melanomas have been included in larger studies of checkpoint inhibition in mucosal melanoma, but the role of checkpoint inhibitors specifically in anorectal melanoma remains unclear.[21] The introduction of immunotherapy did not influence the modality of surgical management of the primary tumor in our series; a similar distribution of APR and WLE was demonstrated in both pre- and postimmunotherapy era patients. Furthermore, given evidence of the limited efficacy of immunotherapy in anorectal melanoma, surgical resection of locoregional disease with clear margins remains the cornerstone of management.[16] Adjuvant checkpoint inhibitors were used more commonly in patients who required an APR, reflecting a more advanced TNM stage at diagnosis.

Several limitations exist in this study. Due to the rarity of anorectal melanoma, our study cohort spans 63 years. Anorectal melanoma patients tend to be managed in centers with colorectal surgical expertise, but not necessarily disease-specific expertise, and the decision-making paradigm may differ between institutions. This may also limit central data acquisition at the MIA. Changing melanoma treatment guidelines and the advent of novel systemic therapies resulted in a heterogenous regimen for adjuvant therapies, of which only a small number of patients were managed in the immunotherapy era. In addition, early checkpoint inhibitor trials excluded patients with mucosal melanoma, limiting access to immunotherapy in this cohort until it became more widely available. There was variable reporting of pathological characteristics for some patients, including tumor thickness and perineural

and lymphovascular invasion, which may be attributed to changes in clinicopathological staging guidelines. Due to the retrospective nature of the database, performance status and comorbidities were not recorded for all patients.

CONCLUSIONS

This study documents the management of anorectal melanoma patients in a single, high-volume melanoma center across a long time period and highlights the need for centralized management to improve our understanding of the disease. Surgery has a continued and pivotal role in the locoregional management of anorectal melanoma, with considerations for associated morbidity and potential impacts on patients' quality of life. Future studies will include additional patients who have received immunotherapy to determine the most appropriate modes of management for patients with anorectal cancer in the current era.

Of greater urgency is the need to develop more effective systemic therapies for mucosal melanoma and examine modes of resistance to current treatments. Despite overall lower response rates, some patients with mucosal melanoma do respond to immunotherapies, raising the possibility that neoadjuvant therapy may improve outcomes in future patient cohorts. Perhaps a neoadjuvant approach could facilitate less extensive surgery in the first instance, with completion APR and lymphadenectomy being reserved for patients with a pathological nonresponse or local recurrence after WLE. We would encourage the oncology community to actively participate in study design and implementation to advance outcomes for patients with this vexing disease.

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