

Case Report

## Outcomes of Surgical Treatment for Patients with Anorectal Malignant Melanoma; Results of Nine Cases in a Single Institution

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### Abstract

Anorectal melanoma (AM) is a rare and aggressive malignancy. Two main types of surgical approach for AM are abdominoperineal resection (APR) and wide local excision (WLE). Nine patients with AM underwent surgical treatment between July 2005 and October 2017 at our institution. Two of the patients were diagnosed with localized stage, four with regional stage, and three with distant stage. Laparoscopic APR was performed in six patients with localized and regional stages, whereas palliative APR and/or WLE were performed in those with distant metastasis. Both patients with localized stage lived without relapse for 6.8 years after surgery. One of the patients with regional stage had no relapse during 3.6 years of follow-up. The other three patients had recurrence and died between 6 and 32 months after surgery. The median overall survival (OS) of the cohort was 14.8 months, and the 5- and 10-year OS were 33.3% and 16.7%, respectively. The tumor at the regional stage could be removed through WLE, but preoperative diagnosis of lymph node metastasis is difficult in patients with AM. Further development of the diagnostic method is expected, and future tasks will be to establish the selection criteria to determine which surgical approach is optimal for this devastating disease.

### Keywords

anorectal melanoma, mucosal melanoma, abdominoperineal resection, laparoscopic surgery

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### Introduction

Both cutaneous and mucosal melanomas originate from melanocytes or melanoblasts; however, the clinical behaviors of the two diseases are markedly different. The incidence of mucosal melanoma is reported to be 1%-2% of all melanomas[1,2], and the prognosis of mucosal melanoma is poorer than that of cutaneous melanoma[3]. In recent years, new treatments targeting the immune system, such as nivolumab (a programmed cell death-1 checkpoint inhibitor) and

ipilimumab (a cytotoxic T-lymphocyte antigen-4 checkpoint inhibitor), have been developed. The use of these new drugs for mucosal melanoma is promising[4], but surgery remains a mainstay for initial treatment[1].

The anorectal tract is the most frequent site for mucosal melanoma in the gastrointestinal tract. The incidence of anorectal melanoma (AM) accounts for 23.8% of all mucosal melanomas[1], and represents 0.05% of all malignant colorectal neoplasms[5]. The median overall survival (OS) of AM was reported to be between 8 and 19 months, and

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**Table 1.** Clinicopathological Features and Prognosis of the Nine Patients.

Case	Age (years)/sex	Stage	Surgery	Depth of the tumor	Relapse	Chemotherapy	RFS	OS	Prognosis
1	46/male	Localized	APR	Tis	No	None	15 yr 1 m	15 yr 1 m	Alive
2	61/male	Localized	APR	Tis	Yes	None	6 yr 10 m	7 yr	Dead
3	70/female	Regional	APR	T1	No	None	3 yr 7 m	3 yr 7 m	Alive
4	84/female	Regional	APR	T1	Yes	DAV, DTIC	1 yr	2 yr 8 m	Dead
5	75/female	Regional	APR	T2	Yes	Nivolumab	3 m	6 m	Dead
6	67/female	Regional	APR	T2	Yes	Nivolumab	1 m	9 m	Dead
7	45/male	Distant	APR	T2	-	Nivolumab, ipilimumab	-	7 m	Dead
8	58/female	Distant	WLE, APR	T4b	-	DAV, DTIC	-	1 yr 2 m	Dead
9	74/male	Distant	WLE	T2	-	DAV, DTIC	-	5 m	Dead

APR; abdominoperineal resection, WLE; wide local excision, DTIC; dacarbazine, DAV; dacarbazine, nimustine, and vincristine.

RFS; relapse-free survival, OS; overall survival

the 5-year OS was 10%-20%[6,7]. Optimal treatment has not been fully clarified because of the rarity and aggressive character of AM. According to the operative approach for AM, the two main types of surgeries are abdominoperineal resection (APR) and wide local excision (WLE). Some authors concluded that radical surgery did not improve OS and WLE was recommended[8,9], whereas others advocated that APR contributed to a better relapse-free survival (RFS) for patients with localized tumors[10,11]. Between July 2005 and October 2017, nine patients with AM underwent surgical treatment at our institution. There was no patient who received chemotherapy without surgery in this study period. This case series aimed to assess the outcomes of the patients who underwent surgical resection for AM at our institution.

### Case Report

All patients were diagnosed with AM by biopsy before surgery. The tumor stage was defined as localized when the tumor growth was limited to the bowel wall. Regional stage tumors had regional lymph node involvement, and distant stage tumors had metastatic disease. The depth of tumor infiltration was classified according to the staging of colorectal cancer (8th edition of the Union for International Cancer Control [UICC]). OS was defined as the time from the date of surgery to the date of death or last follow-up. RFS was defined as the time from the date of surgery to the date of relapse or censored at the time of last follow-up. This study was approved by the institutional review board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (approval code: 2020-1186) and conducted in accordance with the Declaration of Helsinki and all its amendments. All the patients included signed a comprehensive consent form prior to surgery.

Table 1 shows the clinicopathological features and prognoses of the cohort. The study population comprised four

men and five women, with a median age of 67 (range, 45-84) years. Two patients (22%) had localized disease and both of them had melanoma in situ. Four patients (45%) had regional lymph node metastasis, and three patients (33%) had distant disease. Two patients with localized stage presented with no symptoms and the tumors were detected by screening colonoscopy. All patients with regional stage presented with melena. One patient with distant stage presented with bleeding from the anus, and another two patients presented with bleeding and prolapse of the tumor through the anus. The median follow-up period was 9.5 years for survivors, and the median OS of the cohort was 14.8 (range, 4.8-183.7) months. The 1-, 3-, 5-, and 10-year OS were 55.6%, 33.3%, 33.3%, and 16.7%, respectively.

Laparoscopic APR was performed in six patients with localized and regional stage, and R0 resection was achieved in all patients. The median OS of the six patients was 37.9 months, and the 3- and 5-year OS were 50.0% and 25.0%, respectively. The median RFS was 28.3 months, and the 3- and 5-year RFS were 50.0% and 25.0%, respectively. Of the two patients with localized stage, one patient was alive without evidence of disease 15 years after surgery (case 1). Another patient presented suddenly with right hemiplegia and aphasia 6.8 years after surgery. Multiple metastases in the brain, liver, and bones were detected, despite undergoing an annual follow-up. The patient died 2 months after recurrence (case 2).

For one of the four patients with regional stage, no evidence of the relapse was found after 3.6 years of extensive follow-up (case 3). The other three patients developed distant metastases 1, 3, and 12 months after the surgery (cases 4-6). Two of the three patients had local recurrence and distant metastases. Although chemotherapy was administered, the patients died between 3 and 20 months after the detection of recurrence. The median OS and RFS of the four patients with regional stage was 20.5 and 7.9 months, respectively. The 3-year OS and RFS were both 25.0%.



**Figure 1.** In case 7, the huge tumor prolapsed through the anus.



**Figure 2.** Laparoscopic abdominoperineal resection was performed for the patient with anorectal melanoma with a huge tumor.

Palliative surgery was performed for three patients with distant metastasis (cases 7-9). One patient underwent laparoscopic APR, because the tumor enlarged and prolapsed through the anus (Figure 1, 2) after treatment with nivolumab, regorafenib, and ipilimumab (case 7). Another patient underwent trans-anal WLE because of bleeding from the tumor. Although combination chemotherapy was administered, multiple brain metastases and local recurrence were detected. Then, laparoscopic APR was performed because of anal pain and bowel obstruction (case 8).

### Discussion

In the present case series, three of six patients with AM with localized or regional stage were alive for over 3 years after radical surgery, whereas three patients with regional stage developed early relapse within 12 months. The following facts were obtained from the results of this analysis; some patients with AM with a regional stage would benefit from radical surgery.

The most unpleasant feature of AM is its aggressive clinical behavior, including early metastasis, resistance to chemo- and radiotherapy, and poor prognosis. The recent development of immune checkpoint inhibitors provides a promising approach in the treatment of cutaneous melanoma; however, the efficacy of these newer agents in AM is yet to be fully established and controversy remains regarding the optimal management of this rare and aggressive disease. According to the surgical treatment for AM, the goals of surgical intervention may differ according to the stage at diagnosis. In patients with AM with localized and regional stages, a previous study demonstrated that patients receiving any surgical treatment had better prognosis than those receiving nonsurgical interventions[12]. Conversely, surgical resection had no prognostic benefit in patients with AM with distant stage[12]. Palliation of symptoms may be the main purpose

of surgical intervention for patients with AM with distant stage. In the present study, two of three patients with distant stage underwent palliative laparoscopic APR because of anal pain and the prolapse of a huge tumor.

Complete resection in patients with AM with localized and regional stages has been associated with a significant better OS[7,12], and surgeons perform either APR or WLE for treatment. However, the optimal procedure for the management of AM without distant metastasis remains controversial. Regardless of the surgical technique employed for the management of patients with AM with localized and regional stages, it is crucial to obtain a clear resection margin. If the tumor was removed completely, OS was similar between the patients who underwent APR and those who underwent WLE[13]. Therefore, previous authors recommended WLE as an initial surgery for AM that can be resected with negative margins[13]. However, controversy remains as to whether WLE can be used as an initial treatment in patients with mesenteric lymph node involvement. A previous study revealed the prognostic significance of nodal involvement in AM[14]. However, preoperative diagnosis of lymph node involvement is difficult in patients with AM and pathological confirmation of lymph node metastasis is impossible in patients after WLE. When WLE was performed for patients with regional stage, metastatic lymph nodes remained and recurrence was more likely to occur[7]. In our study, two of the nine patients were in the localized stage, and the tumors of the two patients could be removed through WLE. However, four of the nine patients were classified as regional stage after APR, and lymph node metastases were correctly diagnosed in two of the four patients preoperatively. Moreover, one of the four patients with regional stage had no relapse for 3 years after APR; WLE would be insufficient for this patient. Identifying the patients who would benefit from particular procedures is important. Ac-

cording to the preoperative diagnosis of lymph node involvement, Falch et al. showed the superiority of positron emission tomography (PET) over computed tomography in detecting lymph node metastasis and distant metastasis[11]. Although PET was used in two patients with regional stage in this study, 18F-fluorodeoxyglucose uptake in mesenteric lymph nodes was not observed. Correct preoperative staging is necessary to determine which surgical approach is optimal, and further developments of the diagnostic method are expected.

Cumulative results from previous studies have demonstrated several poor prognostic factors, including lymph node metastasis, amelanotic character, male sex, tumor size, depth of tumor infiltration, and others[13,14]. However, the results differed between these studies and no definitive prognostic parameters have been identified. The lack of definitive parameters forced previous studies to choose between APR and WLE for all patients with AM. If there are some clinical parameters, surgeons can distinguish the patients who will benefit from APR or WLE. Chae et al. have demonstrated the long-term outcomes of patients with AM with localized and regional stages[15]. All patients with a regional stage underwent APR, and their 5-year OS and RFS were 43% ± 12%, and 39% ± 12%, respectively. The study population was reclassified by rectal TNM, according to the 7th UICC staging system. The 5-year OS of patients with AM with TNM stage IIIA was 67% ± 19%. Conversely, the 5-year OS of patients with AM with TNM stage IIIC was 0%. The long-term outcomes of the study were good, and patients with AM with TNM stage IIIA might be good candidates for radical surgery. Three of our four patients with regional stage were TNM stage IIIA, and the remaining one was TNM stage IIIC. One patient with stage IIIA was the sole survivor, and another two were dead within 10 months after surgery. Further research is needed to confirm these results, and as mentioned above, accurate preoperative staging is essential to employ this strategy.

In this case series, APR contributed to the long-term survival of one of four patients with AM with a regional stage. Future tasks will be to develop preoperative staging methods, and to establish the selection criteria to optimize surgical management. However, surgical interventions are not enough to control this aggressive disease, and more effective chemotherapy regimens are required.

#### Conflicts of Interest

There are no conflicts of interest.

#### Author Contributions

All coauthors contributed substantially to this study and fulfilled the requirements for authorship as per the guidelines of the International Committee of Medical Journal Editors. All authors have read and approved the final version of

the manuscript.

Approval by Institutional Review Board (IRB)

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