ASTR

REVIEW ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
http://dx.doi.org/10.4174/astr.2014.87.3.113
Annals of Surgical Treatment and Research

# The clinical features and optimal treatment of anorectal malignant melanoma

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Anorectal malignant melanoma (AMM) is a very rare and aggressive disease. The purpose of this article is to review the clinical features of AMM, to understand treatment options, and optimal therapy by reviewing pertinent literature. Traditionally an abdominoperineal resection (APR) sacrificing the anal sphincter has been performed for radical resection of cancer, but recently, wide excision of AMM is attempted since quality of life after surgery is an important issue. Some authors reported that there was no difference in five-year survival between the patient who underwent an APR and wide excision. The goal of both APR and wide excision was to improve survival with R0 resection. Adjuvant chemoradiation therapy can be performed to achieve an R0 resection. AMM shows very poor prognosis. At this time, research on AMM is insufficient to suggest a treatment guideline. Thus, treatment options, and a therapeutic method should be selected carefully.
**[Ann Surg Treat Res 2014;87(3):113-117]**

**Key Words:** Melanoma, Skin neoplasms, Anal neoplasms, Surgery, Wide local excision

## INTRODUCTION

Anorectal malignant melanoma (AMM), which has rare incidence, is as less than 0.05%–4.6% of anorectal malignancies [1,2]. Every year, 76,000 people are newly diagnosed with melanoma in America, and among them 6,100 are diagnosed as mucosal melanoma, which is 0.38% of newly diagnosed cancer patients in America [3]. In Europe, 47,241 people are newly diagnosed with malignant melanoma of the skin, and its incidence rate is 11.4% [4]. Seventy-nine AMM cases were reported for 10 years in Japan, and they showed very poor survival [5]. AMM has a very poor prognosis, with a 5-year survival rate between 6%–22% [6-9]. The management of AMM is challenging. Due to its low incidence, AMM has not been studied well, and most of the publications are case reports or series. Although various treatment modalities for AMM have been suggested including surgical resection, chemotherapy, and radiotherapy, all of them are debatable and evidence is insufficient. Moreover, a randomized controlled trial is impossible in AMM due to its rarity.

When we review the articles concerning about AMM, the physiologic and medical features of AMM are described in similar detail in most articles. Although every article agrees that the initial treatment of AMM should be surgical resection, the method of surgical resection has many debates among the many authors. In Korea, there have been several case reports and review articles of AMM, though the ideal option for surgical excision is not concluded [10]. This review aimed to review the management of AMM in current studies in order to better understand AMM.

**Received** February 4, 2014, **Revised** March 30, 2014,
**Accepted** March 31, 2014

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## INCIDENCE AND CLINICAL MANIFESTATIONS

AMM is a very rare disease and accounts for less than 0.05%–4.6% of all anorectal malignancies [1,2]. AMM is the third most common primary origin of melanoma following skin and retina [2]. Malignant melanoma arising in anorectal lesions accounts for 0.4%–1.6% of all malignant melanomas [11]. AMM patients are more frequently female [6,11,12,14,15], and the median age at diagnosis is 60 years or higher [6,11,12].

The main complaint of an AMM patient is not specific compared with other anorectal benign or malignant disease. The most frequent symptom of AMM patient is bleeding (54%–78%) [6,7,11]. Other symptoms include mass (12%–16%) [6,7,11], pain (14%–27%) [6,7,11], obstipation (6%) [11], diarrhea (4%) [11], and pathologic diagnosis after a hemorrhoidectomy (8%–16%) [7,11]. Moreover, AMM is sometimes diagnosed by a routine health check-up without any symptoms [16]. In the literature review, more than 50% of patients complained of rectal bleeding. Due to delayed diagnosis and the aggressive nature of AMM, 37% of the patients already had distant or regional metastasis at the time of diagnosis [17]. Weinstock [14] reported that at the time of diagnosis only 37% of AMM is confined at the anorectal area, 41% has regional spread and 22% has distant metastasis. Lymphatic spread is common and tends to involve mesenteric and inguinal lymph nodes [18]. The major sites of distant metastasis are lung, liver, and bone [18]. The brain is the most common metastasis site, followed by liver and lung [19].

## SURGICAL TREATMENT

The treatment of AMM has not been standardized due to low incidence and lack of evidence. For now, treatment results are evaluated by survival rates alone [20]. There are various treatment modalities of AMM, including surgical excision, chemotherapy, radiation therapy, and immunotherapy. However, there is no definite treatment of choice.

Generally, surgical excision is considered a primary treatment option for AMM. Traditionally, APR is regarded as the standard surgery for AMM [7,21,22]. APR is preferred because it can control lymphatic spread (mainly to mesenteric lymph nodes) and guarantee a larger negative margin for local control [23]. Ishizone et al. [2] reported that APR with lymph node dissection should be performed because of regional lymph node metastasis if there is submucosal invasiong (T1). However, due to high morbidity and mortality of APR, Wide local excision (WLE) is also advocated by some authors [12,20,23,24]. WLE has many benefits such as quicker recovery, minimal impact on bowel function and no need for a stoma [18]. Some reports suggest that APR leads to complications such as urinary and sexual dysfunction and has no advantage over WLE [18,25]. However, Ramalingam et al. [13] documented that laparoscopic APR could control disease and reduce morbidity at the same time. Between the two groups who underwent APR and WLE, there was no difference in five year survival rates [7-9,25-27].

Bullard et al. [25] reported that APR has no benefit for locoregional recurrence and systemic recurrence compared to WLE. This means that most recurrences occur systemically regardless of the initial surgical procedure [18]. Locoregional recurrence of AMM occurs more at the inguinal lymph nodes than at the pelvic lymph nodes [9]. Neither APR nor WLE affect any of the inguinal lymph nodes, therefore neither of them offers an advantage in controlling locoregional recurrence [9,28]. However, it is important to achieve a negative resection margin irrespective of the surgical method performed for local control [28]. WLE with successful R0 resection could show better survival than APR [28]. WLE is curative for stage 0 disease and would be proper concerning the quality of life.

The depth and size of tumor is one of the important prognostic factors. If the lesion is thick (>3 mm) and large (>30 mm), curative surgery cannot be achieved [29]. In this case, conservative local excision and adjuvant therapy can result in a better prognosis [6]. At the time of diagnosis, if AMM is already in the advanced stage, surgical options should be selected based on quality of life [30]. For advanced stage, WLE with adjuvant radiotherapy and biochemotherapy could be done concerning favorable functional outcome and longer median survival.

Conclusively, most authors suggest that WLE should be the first treatment of choice if surgically feasible, and APR would be the palliative method when there is obstruction and need for salvage surgery [19,24,31].

## RADIOTHERAPY

Adjuvant radiation therapy after surgical excision has also been attempted. Radiotherapy to extended field followed by sphincter saving wide excision reduced locoregional recurrence rate to 17% from 50% compared to WLE alone [32]. In comparison to APR, WLE with adjuvant radiotherapy achieves equal locoregional control [33]. In fact, extended radiation therapy to the pelvic/inguinal lymph nodes is associated with serious complications such as lymphedema and proctitis [32,34]. Preoperative neoadjuvant radiotherapy demonstrated only minimal effect on local tumor burden [34]. Adjuvant radiotherapy can decrease locoregional recurrence, but distant relapse, which cannot be controlled, is the main cause of death [32]. Gupta et al. [35] investigated interstitial brachytherapy with caesium-137 and analyzed its ability to prevent local recurrence.

## CHEMOTHERAPY

Currently, a standard therapeutic regimen for chemotherapy

in the setting of AMM does not exist. In addition, the rarity of AMM makes it difficult to evaluate the clinical efficacy of systemic therapy [36]. Many regimens, including dacarbazine, Bacile Calmette-Gurin (BCG), levamisole, cisplatin, vinblastine, intereukin-2 and interferon, have been investigated [16,25]. These regimens are based on drugs developed for advanced cutaneous melanoma [16].

## OTHER TREATMENTS

Recently, the use of immune-modulating agent for cancer treatment has increased, since chemotherapy or radiotherapy alone is insufficient to completely eradicate AMM. Moreover, immunotherapy can boost anticancer immunity [37]. Immunochemotherapy is a chemotherapy regimen which includes an immunologic agent. Immunochemotherapy includes specific active immunization and adoptive immunotherapy based on antigenic system [38]. The response rate of dacarbazine, which is one of the most effective agents for metastatic melanoma, is only 20% [23,39]. Immunochemotherapy use with cisplatin, vinblastine, dacarbazine, interferon alpha-2b and interleukin-2 demonstrated similar overall response and complete response rates to that of advanced cutaneous melanoma [36]. Phade and Lawrence [40] reported a case review of immunochemotherapy (dacarbazine, BCG) with encouraging results. When comparing patients treated with and without biochemotherapy, the former group showed a longer median survival [36].

A newly developed agent, temozolomide, demonstrates equivocal efficacy to dacarbazine and is an oral alternative for advanced metastatic melanoma [41]. Yeh et al. [42] administered a combination of temozolomide, cisplatin and liposomal doxorubicin (intrahepatic infusion to liver metastasis) in a patient whose primary lesion was unresectable, and regression of the primary and metastatic tumors was confirmed.

## PROGNOSIS

The prognosis of AMM is very poor due to its aggressive characteristics. The five year survival rate of AMM is 6%–22% [6-9], and the median survival in the literature is 19–26.4 months [6,7,26]. The five year survival rate varies according to the presence of metastasis. If AMM is confined to the local area, the five year survival rate is 37%–50% [14,17]. However, if there is regional and distant metastasis, the five year survival rate decreases in 7%–17% and 0%–6%, respectively [14,17]. Though the prevalence of AMM in women is higher, the overall survival was longer in women compared to men (15.7% and 10.6%, respectively) [28].

The prognosis of AMM differs depending on the stage of AMM. There is no specific system for staging of AMM at this point. Ross et al. [9] classified AMM patients into three stages; stage I (localized disease), stage II (regional disease), and stage III (with distant metastasis). According to this staging system, stage I was associated with better survival results than stage II or III [26]. Concerning cutaneous melanoma, (1) thickness of cancer, (2) mitotic rate, and (3) presence of ulceration are the most important prognostic factors [43]. The thickness of the tumor proves to be an influential factor in AMM, and thickness less than 2 mm is the major factor for determining long-term survival [6,8,23,44]. In AMM, ulceration is frequently seen on examination of the gross specimen of AMM [36]. It has been proven by various institutions that the tumor depth has a significant effect on the survival rate [23,45,46]. The size of the tumor can also determine the survival [7]. In addition, the nodal status at the time of diagnosis is another predictive factor [23]. At the time of diagnosis, a patient with nodal metastasis had decreased five year disease-specific survival, disease-free survival and distant metastasis-free survival compared to those patients without nodal metastasis [33]. Duration of the initial symptom also influences the prognosis [23]. As the initial symptom is similar to that of hemorrhoids, clinicians often look over it as a common benign disease. Therefore diagnosis of AMM is frequently delayed [36].

The relationship between the tumor location and prognosis is unclear at this point. If the tumor locates proximal to the dentate line, the disease showed an advanced stage more than the distal tumor. If the tumor is located proximal to the dentate line, the disease stage is more advanced than if the tumor is located distal to the dentate line. However, if the tumor is located distal to the dentate line, the lymph node recurrence rate is higher than if the tumor is proximal to the dentate line. Therefore, the overall prognosis of the two groups is not significantly different [47].

As mentioned before, nodal metastasis can be a prognostic factor of AMM. If R0 resection is not successful and metastatic lymph nodes remain, regional recurrence is more likely [28]. However, prophylactic lymph node dissection for every patient is too risky due to the complexity of the procedure [18]. Sentinal lymph node mapping (SLNM) is used in cutaneous melanoma to determine the extent of excision. SLNM could potentially be used in AMM. In the circumstance of pathologically positive nodal metastasis but clinically negative nodal metastasis, SLNM can prevent understaging [18]. SLNM can also aid in planning the extent of surgery [48].

## CONCLUSION

AMM has no treatment guidelines currently, the choice of therapeutic method should be carefully considered. Early diagnosis and a tailored, multidisciplinary treatment plan would likely improve the treatment result of AMM. Large scale

prospective clinical trials should be conducted in the future to investigate effective treatments for AMM.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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