Primary anorectal malignant melanoma: rare but highly lethal malignancy

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Aim: Primary anorectal malignant melanoma (MM) is a rare but highly lethal malignancy. The aim of this study was to present an overview of the clinical features and treatment strategies in patients with anorectal MM.

Materials and methods: Nine patients who were diagnosed with anorectal MM between 1998 and 2010 were reviewed retrospectively.

Results: The median age of the patients was 51 years (range: 28–75). The sex ratio of male to female was 1:2. The main presenting symptom was rectal bleeding. At the time of diagnosis, 1 patient was stage IV and 8 patients were stage III. All of the patients underwent an abdominoperineal resection. Only 1 patient received adjuvant immunotherapy and 8 patients received palliative immunotherapy or dacarbazine and/or platinum-based chemotherapy. The median progression-free survival was 31 weeks (range: 6–211). Sites of metastasis were the lung, liver, and brain in order of frequency. The median overall survival was 81 weeks (range: 54–229).

Conclusion: Clear guidelines for the therapy of anorectal MM have not been established. In the treatment plan of primary anorectal MM, multimodal treatment options involving surgery, radiotherapy, and systemic treatment with chemotherapeutics or biological agents should be considered.

Key words: Anorectal region, malignant melanoma, treatment strategies

Introduction

Malignant melanoma (MM) is usually derived from melanocytes producing skin pigmentation. Even though MM constitutes only 4% of all skin malignant neoplasms, it is responsible for 80% of the deaths due to cutaneous neoplasms. Aside from the cutaneous area, MM may also be observed in the eyes, mucosal sites of the gastrointestinal system, the head and neck area, and genital regions in the order of frequency.

There are also very rare subcategories of mucosal MM, such as desmoplastic MM of the gingiva and intestinal MM (1,2).

The anorectal region is the most frequently affected part of gastrointestinal system MM. MM in the anorectal area often develops from melanocytes that are in the nonkeratinized squamous epithelium, under the dentate line and transitional epithelium. Anorectal MM constitutes 0.4% to 1.6% of all
melanomas and less than 1% of anorectal tumors. MM is more common in women than in men and usually occurs in the 5th to 6th decades of life (3). Patients with anorectal MM are usually admitted to hospitals with the clinical symptoms of rectal bleeding, anal mass, and changes in defecation habits (4). Anorectal MM is frequently diagnosed in the advanced stage, since most symptoms are nonspecific or because a loss of time due to the treatment strategies for hemorrhoidal disease has occurred (5).

Histopathological examination and immunohistochemical studies are of great importance in the diagnosis of anorectal MM. Positive protein S-100, melanoma antigen HMB-45, and melan-A expression strongly support the diagnosis of melanoma (3).

Well-described surgery and adjuvant treatment principles are available for cutaneous MM. However, cutaneous MM treatment principles cannot fully be applied to anorectal MM. Moreover, guidelines for the treatment of anorectal MM are absent due to the rareness of the disease and the inability to form large, homogeneous series for randomized trials.

This study was presented with the purpose of sharing our treatment experiences of patients with anorectal MM and reviewing the clinical specifications, follow-up, and treatment strategies of the patients based on English-language literature.

Materials and methods
In this study, 9 anorectal MM patients, diagnosed between 1998 and 2010, were reviewed retrospectively. Age, sex, presenting symptoms, stage at the time of diagnosis, sites of metastasis, surgery, and treatment modalities were recorded.

Results
The median age of the 9 patients was 51 years (range: 28–75). Six patients (67%) were female. Six patients (67%) presented with rectal bleeding, 2 with sensation of anorectal mass, and 1 with anal pain. At the time of diagnosis, 1 patient had stage IV disease and 8 patients had stage III disease with lymph node metastasis. All of the patients, including the metastatic patient, had undergone an abdominoperineal resection (APR). Only one patient received adjuvant immunotherapy.

The median follow-up was 81 weeks (range: 54–229). All of the patients developed distant metastasis within the follow-up period. The median progression-free survival (PFS) was 31 weeks (range: 6–211). Visceral sites of the metastasis were the lung, liver, and brain in the order of frequency. All but one of the patients died during the follow-up period. The median overall survival (OS) was 81 weeks (range: 54–229).

The patients received a minimum of 1 and a maximum of 4 lines of palliative chemotherapy or immunotherapy. In the metastatic setting, 4 patients (44.4%) received dacarbazine (DTIC) and cisplatin, 1 received temozolomide (TMZ), 1 received DTIC alone, and 3 received interferon (IFN) as the first-line treatment. In the second line, 4 patients (80%) received TMZ and 1 received paclitaxel and carboplatin (PC). In the third line, 3 patients received PC. In the fourth line, 1 patient received IFN (33.3%), 1 received DTIC, and 1 received ipilimumab with an early access program.

Palliative radiation therapy was used for 4 patients (1 (25%) for brain metastasis, 1 for brain and intraabdominal lymph node metastasis, and 2 for the primary site of the rectum).

The general characteristics of the patients are shown in the Table.

Discussion
Anorectal MM is an aggressive neoplasm seen in the 5th and 6th decades of life with a female preponderance. The most frequent symptom leading to diagnosis is rectal bleeding. The feeling of an anorectal mass, anal pain, discharge, and/or itching may be among the other initial symptoms. Patients are unusually misdiagnosed as having hemorrhoidal disease due to these nonspecific symptoms; thus, the main diagnosis is frequently delayed (3,5).

In this study, similar to in the literature, the median age of the entire cohort was 51 and the female-to-male ratio was 2:1, with the most frequent initial symptom being rectal bleeding. In the only patient who was presented in the upfront metastatic stage,
The diagnosis was delayed because of the symptoms resembling hemorrhoidal disease.

The reported incidence of locoregional lymph node metastasis at the time of diagnosis was 61% in the anorectal area, 21% in the head and neck area, 23% in the genital area, 11% in the urinary system, and 9% in skin/cutaneous melanoma (6). Parallel to the literature, 8 of the 9 anorectal MM patients in the present study had locoregional metastasis. Therefore, it can be concluded that the prognosis of anorectal MM is noticeably worse than both adenocarcinoma of the same region and MM of the cutaneous origin.
In addition to the advanced stage at the time of diagnosis, the rich vascularity of the rectum and the biological aggressiveness of the tumor were also blamed for the poor prognosis (7).

The traditional treatment of anorectal MM is usually based on surgery. Surgical treatment options include radical operations such as APR, pelvic exenteration, or conservative methods such as local excision (LE). Wide LE is recommended as the primary therapy if negative resection margins can be achieved (8). Iddings et al. (9), who presented the largest series in this respect with 183 patients, reported that radical operations were gradually decreasing in number and were the less preferred method of surgery. There are numerous studies searching for the effects of radical and conservative methods on survival. Most of these studies reported that radical resections did not contribute to prolonged survival (8,10,11). However, a poor prognosis was confirmed despite the curative surgical approach of anorectal MM in a retrospective analysis with either APR or LE (12). In addition, one must not forget that survival is determined by distant metastasis. LE may prevent a gross surgery and complications due to colostomy, but it is evident that there is no choice other than radical surgery in diseases appearing with serious bleeding or obstructive large or anal sphincter invasive tumors. We speculate that APR was obligatory in our patients because of quite serious anorectal grievances such as bleeding and advanced staging. Determination of the optimal surgery option should aim not only to extend the lifetime but also to increase the quality of life.

Recent studies revealed that adding locoregional radiotherapy (5 × 6 Gy) to sphincter-sparing surgery provided less loss of function when compared to APR, and similar locoregional control was obtained (13). In this study, APR was applied to all of the patients; thus, radiation therapy was not used for local control.

While standard staging and adjuvant treatment suggestions for skin MMs are specified, standard guidelines for staging and adjuvant treatment protocols for anorectal MM are not specified. Actually, it is already known that anorectal MM is quite radioresistant and does not respond well to chemotherapy. Despite having no proven benefit, adjuvant treatment protocols used for skin MMs are not infrequently used for anorectal MM patients.

Many agents have been tried in the adjuvant treatment of cutaneous MM, but a clinical benefit was only obtained with alpha-IFN 2b and pegylated forms of IFN (14). In this study, 69 weeks of disease-free survival was obtained in 1 patient, to whom IFN was given in the adjuvant setting.

Chemotherapy is generally used for palliative purposes in advanced stages of MM and survival after diagnosis is quite short. There are standard systematic treatment options defined in advanced cutaneous MM patients, including cisplatin, vinblastine, DTIC, IFN, and interleukin-2. In many studies conducted in the last decade, single agent or combination chemotherapy regimens for advanced stages of skin MMs were tried; however, DTIC has still been accepted as the standard of care (15). Because of the limited number of studies, there is no standard treatment for mucosal MM (16). DTIC was used as a single agent or in combination as the first line of treatment at the metastatic stage in our series.

Another alternative is an orally bioavailable drug, TMZ. It does not require hepatic activation and quickly passes through the blood–brain barrier. In a phase III study by Middleton et al. (17), an equal efficacy of TMZ in comparison to DTIC was found in advanced stage metastatic cutaneous MM patients. PFS in patients treated with TMZ was 1.9 months in comparison to 1.5 months with DTIC (P = 0.012; HR, 1.37; 95% CI 1.07–1.75). Another combination chemotherapy commonly used in advanced stage cutaneous MM is the PC combination. Rao et al. (18) used PC in the second line of treatment of cutaneous MM and found a median PFS and OS of 3 and 7.8 months, respectively. In this study, 1 patient who received PC in the second line of treatment showed 7 weeks of PFS, and 3 patients who received PC in the third line of treatment showed 26, 13, and 9 weeks of PFS.

Yeh et al. (16) used a combination regimen with cisplatin as the third line of treatment after colostomy and radiotherapy, TMZ, and liposomal doxorubicin for a 49-year-old female anal mucosal melanoma patient with complete colonic obstruction and multiple distant organ metastases. After the second course, more than 50% regression was observed in the metastases in all regions, and the analgesic need was minimized and the quality of life of the patient
improved with minimal residual disease at the 12th month of treatment.

Research regarding MM treatment has accelerated in recent years. Ipilimumab, which is an immunomodulatory monoclonal antibody, was developed against an antigen on T lymphocytes. Common T lymphocyte antigen-4, an antigen that is related to cytotoxic T lymphocytes, has a pressurizing function on cytotoxic T cells. Blocking this antigen results in cytotoxic T cells' movement against cancer cells. A 3-arm phase III randomized study by Hodi et al. (19) demonstrated that ipilimumab increased survival in 674 pretreated patients with advanced stage cutaneous MM.

Ipilimumab is accepted as an alternative treatment option for patients with resistant cutaneous MM, but its place in primary anorectal MM treatment should be further studied.

In a study of 17 anorectal MM patients, the median OS was reported to be 32 weeks. In that study, 7 patients were treated with radical surgery, and only 2 patients received adjuvant immunotherapy (20). The reason for the longer OS data of the present study may depend on the application of radical surgery to all of the patients or the adding of more systemic palliative treatment lines (like PC or ipilimumab) before following up with the best supportive care.

Presently, advanced anorectal MM remains an incurable disease, and despite the use of multidisciplinary strategies (radical surgery, immunotherapy, chemotherapy, and radiotherapy), it remains a fatal disease. Current guidelines do not include a definitive staging or standard treatment options for anorectal MM. As a result, treatment of individual cases is based on retrospective studies including a limited number of cases. Surgery still remains the mainstay of the treatment. Adding radiotherapy, systemic treatment with immunotherapeutics and/or chemotherapeutics, or biological agents to surgery should be considered since the prognosis of anorectal MM is dismal.

References
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