Anorectal melanoma: experience from a tertiary cancer care centre in South India

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ABSTRACT

INTRODUCTION Mucosal malignant melanoma of the anorectum is a rare and aggressive disease, in which early diagnosis is difficult. The prognosis remains extremely poor, irrespective of the treatment. We share our experience in treating this malignancy at our centre in South India.

METHODS This study describes a retrospective analysis of 31 cases of anorectal melanoma presented to our centre between January 2001 and December 2013.

RESULTS Twenty-two patients (71%) presented with metastasis and had a median overall survival of nine months. None of the 22 patients survived for two years. Nine patients (29%) had curative surgery, in the form of abdominoperineal resection (six patients), abdominoperineal resection with bilateral inguinal node dissection (one patient), abdominoperineal resection with liver resection (one patient) and posterior exenteration (one patient). In patients who underwent curative surgery, the median overall survival was 15 months and disease-free survival was nine months, with a two-year overall survival of 22%.

CONCLUSIONS Anorectal melanoma is an aggressive disease with a poor prognosis. The majority of patients present with distant metastases. Prognosis depends on stage at presentation. Early diagnosis and surgical resection may improve the overall outcome. Newer modalities such as immunotherapy and targeted therapies such as anti-CTLA4 monoclonal antibody and anti-programmed cell death protein 1 monoclonal antibodies have radically changed the management of mucosal melanoma and may, in the future, improve the overall prognosis of anorectal melanoma.

KEYWORDS

Anorectal melanoma – Mucosal melanoma – Anus – Rectum

Accepted 28 August 2017

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Introduction

Anorectal melanoma is a rare tumour with a poor prognosis. It accounts for less than 1% of all anorectal malignancies worldwide.¹ In India, however, it accounts for 2–5% of all cases of anorectal cancer.² The five-year overall survival of anorectal melanoma is in the range of 4–10%, while the median survival varies from 16–28 months.^{3,4} There are no definite recommendations for the management of these lesions. Treatment strategies have varied from the radical abdominoperineal resection to the conservative wide local excision. There are no randomised trials addressing the extent of primary surgical treatment nor the outcomes of adjuvant treatment.

The aim of this study was to analyse the outcome of patients with anorectal melanoma from a tertiary cancer care centre in India.

Methods

We retrospectively analysed 31 patients with anorectal melanoma who were treated in our tertiary care institution from January 2001 to December 2013. The cases were identified from a prospective database with the help of International Classification of Diseases for Oncology site codes for anus and rectum and the morphology code for melanoma. The case records were reviewed in detail regarding the clinical features (symptoms, duration, investigations and stage), pathological features (whether diagnosis of melanoma was confirmed histologically), treatment offered and follow-up details. Missing data regarding treatment follow-up and current status were retrieved in a telephone interview with the patient or relative of the patient.

For the purpose of this analysis, the patients were categorised into two groups – the ‘metastatic group’ and the

‘potentially curative group’– depending on the stage of the disease on presentation. The potentially curative group had disease limited to the primary site and regional lymph nodes (one isolated liver metastasis) which could be addressed surgically with curative intent. The metastatic group of patients had lymphatic spread beyond the pelvis or a distant site of metastasis.

Results

Of the 31 patients studied, 12 (38.7%) were men and 19 (61.3%) were women, with a mean age of 51 years (range 20–82 years); 22 (71%) were in the metastatic group and only 9 (29%) in the potentially curative group. The clinical details are shown in Table 1.

The metastatic group

Among the 22 patients in the metastatic group, the liver was the most common site of metastases (63.6%), followed by the retroperitoneal lymph nodes (31.8%). Seven patients underwent palliative chemotherapy (six patients with dacarbazine and one with temozolomide plus thalidomide). Two patients underwent palliative radiation therapy to the brain for brain metastases. Two patients underwent local palliative radiation therapy. The median survival in this group was nine months (Fig 1). The clinical features and survival of 22 patients in the metastatic group are detailed in Table 2.

The potentially curative group

Of the nine patients in the potentially curative group, eight had locoregional disease and one had a solitary liver metastasis. Abdominoperineal resection was performed in six patients, abdominoperineal resection with bilateral inguinal node dissection in one patient and posterior exenteration in one patient. One patient had solitary liver metastasis in segment 2/3, in whom abdominoperineal resection and left hepatectomy was done. In the potentially curative group, median survival was 15 months (Fig 1) but median disease-free survival was 9 months. In seven of the nine patients

Figure 1 Overall (OS) and disease-free (DFS) survival rates in the two groups studied.

(77.7%), disease recurred at a distant site, with liver being the most common site. Two patients had local recurrences. Patients with disease limited to the submucosa with no lymph node involvement had maximum survival, with a mean survival of 31.5 months. The clinical features of the nine patients in the potentially curative group are shown in Table 3.

Treatment outcomes

Median overall survival in this retrospective cohort was nine months and the two-year overall survival was 6.5%. Median survival was nine months in metastatic group compared with 15 months in the potentially curative group ($P = 0.016$; hazard ratio, HR, 0.45; 95% confidence interval, CI, 0.22–0.91); Fig 1). Two-year overall survival was 22% (two of nine patients) in the potentially curative group whereas none of the patients in the metastatic group survived for two years.

Discussion

Anorectal melanoma is a rare malignancy with a highly aggressive biology. According to the available literature, the incidence in India seems to be higher than in the Western world.⁵ The mean age of presentation in our series was 51 years, which is consistent with many other reported series. In our series, the most common presenting symptom was rectal bleeding. As is seen in previous reports,⁵ the majority (71%) of our patients had extensive metastatic disease at initial presentation, with the most common site of metastasis being the liver. In our series, the prognosis of metastatic disease was dismal, irrespective of the treatment offered, with a median survival of nine months. Median survival of metastatic anorectal melanoma from a similar series of 63 patients was only four months.⁵ In a recent surveillance, epidemiology and end results data analysis, the survival closely

Table 1 Clinical features of 31 patients.		
Feature	Patients	
	(n)	(%)
Symptoms:		
Bleeding per rectum	22	71
Mass per anus	4	13
Bleeding and mass	3	9.66
Painful defecation	1	3.22
Altered bowel habits	1	3.22
Histology:		
Bleeding per rectum	22	71
Mass per anus	4	13

Table 2 Clinical features of 22 patients in the metastatic group.

Patient	Age (years)	Sex	Site of metastases	Palliative treatment offered	Survival (months)
1	70	F	Liver	–	4
2	58	M	Liver	–	8
3	45	M	Liver	–	9
4	37	F	RPLN	850 cGy local radiotherapy	21
5	51	M	Liver, brain	Dacarbazine-based chemotherapy	9
6	33	F	Peritoneal deposits	Dacarbazine-based chemotherapy	11
7	45	F	Liver, brain	Radiotherapy brain	8
8	67	M	Liver	–	9
9	70	M	Liver	–	9
10	56	M	RPLN	–	8
11	82	F	RPLN	–	9
12	51	F	Liver, spine	Dacarbazine-based chemotherapy	7
13	36	F	Liver, mets, RPLN	–	6
14	55	M	Liver	Dacarbazine-based chemotherapy	9
15	63	M	Liver, lung, brain	Radiotherapy brain	2
16	30	F	Pelvic deposits	Dacarbazine-based chemotherapy	3
17	38	M	Peritoneal deposits	Dacarbazine-based chemotherapy	6
18	58	F	Liver, brain	–	11
19	60	F	RPLN	Temozolomide + thalidomide chemotherapy	7
20	56	F	RPLN	–	12
21	49	F	Liver	Radiotherapy 30 Gy/10# local radiotherapy	17
22	64	M	Liver	–	13

F, female; M, male; RPLN, retroperitoneal lymph nodes

paralleled the stage at diagnosis, with a median survival of six months for metastatic disease.⁶

The potentially curative group in this series, which consisted of 29% of the total study population, presented with locoregional disease, except one patient who had a solitary liver metastasis for which liver resection was performed with the primary surgery. All nine patients in the potentially curative group had undergone radical surgery in the form of abdominoperineal resection or posterior exenteration. None of the patients had a wide local excision, so a comparison between these surgical procedures was not possible. Median survival in this group was 15 months, which was comparable to the data analysis by Chen *et al.*⁶

For non-metastatic anorectal melanoma, surgical resection is the traditional standard of care, with patients undergoing surgery showing improved prognosis even though the optimal surgical procedure is still in question.^{7–9} In this study, the patients who presented with a potentially resectable disease had a statistically significant better median survival when compared with those with inoperable disease (15 months vs. 9 months, $P = 0.016$; HR: 0.45; 95% CI 0.22–0.91). However, disease-free survival was only nine months (range

3–18 months). The local recurrence rate was 22.2%, with perineum being the site of the recurrence in the two patients who recurred locally (Table 4).

The most important prognostic indicators in anorectal melanoma include the stage of disease and nodal involvement, in addition to size and duration of symptoms.^{11–14} Two patients with disease limited to submucosa without any nodal disease, who underwent radical surgery, had a mean survival of 31.5 months when compared with a mean survival of 11.7 months in those with higher-stage disease. Invasion beyond submucosa was associated with increased nodal or distant recurrence and a poor survival, although the statistical significance of this observation could not be determined because of the small study size. One patient with a solitary liver metastasis who underwent abdominoperineal resection with left hepatectomy surprisingly survived for 17 months, suggesting the possible role of radical surgery in those with oligometastatic disease.

In this series, none of the nine patients in the potentially curative surgery underwent wide local excision. However Xu *et al.* observed that, even though the rate of local recurrence was slightly higher with local excision when

Table 3 Clinical features of the nine patients in the curative group.

Patient	Age (years)	Sex	Surgery	Depth of infiltration	No. of LNs positive	Total LNs Harvested	Site of first recurrence	DFS (m)	OS (m)
1	48	F	APR	Serosa	7	10	Liver	9	12
2	46	F	APR with bilateral inguinal dissection	External sphincter	Multiple inguinal and perirectal		Perineum	3	4
3	54	M	APR	Serosa	10	10	Liver	15	15
4	58	M	APR	Amelanotic peri-rectal fat	3	12	Perineum	4	16
5	70	F	APR	Submucosa	0	9	RPLNs	14	24
6	20	F	APR	Peri-rectal fat	4	11	Liver mets RPLNs	6	12
7	26	F	Posterior exenteration	Infiltrating posterior vaginal wall	9	11	Liver	3	6
8	53	F	APR	Submucosa	0	8	Lung	18	39
9	44	M	APR with liver resection ^a	Submucosa	1	11	RPLNs	13	17

^a Patient with solitary liver metastasis; left hepatectomy was performed.
APR, abdominoperineal resection; F, female; M, male; RPLN, retroperitoneal lymph nodes.

Table 4 Local recurrence and overall survival in patients undergoing abdominoperineal resection.

Study	Year	Patients (n)	Local recurrence (%)	Median overall survival (months)
Moozar <i>et al.</i> ¹⁰	2003	4	0	12
Bullard <i>et al.</i> ⁴	2003	4	50	14
Ramakrishnan <i>et al.</i> ⁵	2008	3	0	10
Present study	2016	9	22.2	15

compared with abdominoperineal resection, the surgical method does not affect the overall prognosis of anorectal melanoma.⁸ One study which looked at anorectal melanoma over a 64-year timeframe concluded that abdominoperineal resection should be considered in patients with localised anorectal melanoma, particularly those with smaller tumours and no evidence of nodal metastases.¹⁵ In most studies however, wide local excision is a therapeutic option because of its better quality of life, since there is no significant improvement in overall survival with abdominoperineal resection.¹⁶

There are limited data on adjuvant systemic therapy in patients with mucosal melanoma. The adjuvant chemotherapeutic agents used for cutaneous melanoma are cisplatin, vinblastine, dacarbazine, interferon B and interleukin 2.¹⁷ Dacarbazine is the most commonly used single agent and usually initiates a partial response in 20% of patients four to six months after treatment.¹⁹ High-dose interferon (INF-2 alpha) therapy in adjuvant setting for cutaneous melanomas has shown to have statistically significant improvement in

relapse-free survival and median survival, although the overall survival was not significantly improved.¹⁹ The only data on the efficacy of systemic therapy for mucosal melanoma in the adjuvant setting come from a phase II randomised trial of interferon versus chemotherapy in Chinese patients with resected mucosal melanoma.²⁰

New immunotherapeutic agents such as the anti-CTLA4 monoclonal antibody, ipilimumab and the anti-programmed cell death protein 1 (PD-1) monoclonal antibodies (nivolumab, pembrolizumab) have shown to prolong relapse-free survival significantly in patients with cutaneous melanoma. In a phase III randomised trial, the relapse-free survival, distant metastases-free survival and overall survival were significantly better with ipilimumab in adjuvant setting for cutaneous melanoma.²¹ There are no randomised trials with ipilimumab exclusively for mucosal melanoma. A retrospective analysis of 33 patients with unresectable or metastatic mucosal melanoma treated with ipilimumab suggested good response rates.²² The PD-1 monoclonal antibodies nivolumab and pembrolizumab have been shown to prolong the median progression-free survival significantly in patients with mucosal melanoma. Although there are no randomised clinical trials specifically addressing the activity of these agents in patients with mucosal melanoma, these agents have a significantly better overall response rate and progression-free survival.^{23,24}

Our study has its limitations, as it is a retrospective series based on case records. There were no patients who had undergone wide local excision for a comparative analysis. None of the patients were treated with immunotherapeutic agents, as these agents were not in use in our institution during the study period.

Data from two phase II studies reported at the American Society of Clinical Oncology annual meeting in June 2017

lend support to combined use of ipilimumab and nivolumab in metastatic melanoma, which might bring about a change of practice in the future.^{25,26}

Conclusions

Anorectal melanoma is an aggressive disease with a poor prognosis. The majority of patients present with distant metastases. Prognosis depends on stage at presentation. Early diagnosis and surgical resection may improve the overall outcome. Newer modalities such as immunotherapy and targeted therapies such as anti-CTLA4 monoclonal antibody and PD-1 monoclonal antibodies have radically changed the management of mucosal melanoma and may improve the overall prognosis of anorectal melanoma in the future.

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