

Optimizing local control in anorectal melanoma

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Abstract

BACKGROUND: Wide local excision (WLE) of anorectal melanoma is associated with a high incidence of local recurrence. There is a paucity of literature on adjuvant radiation in this malignancy. **AIM:** To identify the optimal method of local treatment in anorectal melanoma. **SETTINGS AND DESIGN:** Retrospective study in a tertiary cancer centre. **MATERIALS AND METHODS:** Records of 63 patients who presented between 1980 and 2004 were reviewed. **RESULTS:** Of the 63 patients, 18 were treated by either surgery with or without adjuvant radiation, or by radiation alone. The remaining had advanced disease and were offered only symptomatic treatment. The median overall survival in stage I patients was 12 months, while it was seven and four months in those with stage II and III disease respectively. The median survival in patients treated by WLE with adjuvant radiation (RT), WLE alone or Abdominoperineal resection (APR) was 34, 12 and 10 months respectively. Patients in whom the disease was confined to the mucosa had a better median overall survival than those in whom it had infiltrated beyond the mucosa (102 vs 11 months). The pattern of recurrence following WLE with adjuvant RT or APR was similar. None of the patients who received adjuvant RT after wide excision had a local or nodal recurrence. **CONCLUSION:** Local treatment of anorectal melanoma should be individualized. WLE with adjuvant radiation seems to offer good locoregional control without reducing the survival and may be an option of treatment for patients with small, superficial anorectal melanoma. However, APR should be offered for patients with locally advanced disease or as a salvage following recurrence.

Key words: Adjuvant radiation, anorectal melanoma, local control, mucosal melanoma

Introduction

Anorectal melanoma is a rare tumor with a poor prognosis. It accounts for less than 1% of all anorectal malignancies.^[1,2] However, in India, they account for 2-4% of all anorectal cancers.^[3] The five-year overall survival in patients with anorectal melanoma ranges from 4 to 31%, while the median survival varies from 16 to 28 months.^[4-11] There are no definite recommendations for the management of these lesions. Treatment strategies have varied from the radical abdominoperineal resection (APR) to the conservative wide local excision (WLE). There are very few studies that have evaluated the role of adjuvant radiotherapy in anorectal melanoma.

Materials and Methods

Between 1980 and 2004, 63 patients with a diagnosis

of anorectal melanoma were evaluated in our institution. These patients were identified from the computer data base in our tumor registry using the ICD-O (third edition) site codes for anus and rectum (C21.0, C44.5 and C20.9) and the morphology code for melanoma (M-8720/3). The case records of these patients were retrospectively reviewed in detail to obtain information regarding clinical features (symptoms, duration, investigations and stage), pathological features (size, depth of invasion and immunohistochemical studies), treatment and follow-up details. Depth of the lesion was assessed either by histopathological examination of the surgical specimen or by clinical examination in patients who did not undergo surgery.

Immunohistochemistry (IHC), performed by the streptavidin-biotin-peroxidase method was used to further categorize anorectal tumors labelled on routine

hematoxylin-eosin staining as poorly differentiated malignancies. IHC studies were performed by the streptavidin-biotin-peroxidase method. The antibodies used for IHC studies included the M0634 mouse antihuman antibody for HMB 45, Z0311 polyclonal rabbit anti-cow antibody for S 100 and M0725 mouse antihuman antibody for Vimentin (all from Dako Cytomation, Denmark).

The patients were classified into stage I (localised disease), Stage II (presence of inguinal or pelvic nodes) or Stage III (distant metastasis), similar to the staging system in vogue for anorectal melanoma.^[4,7] Treatment was based on the extent of disease at presentation. Patients with stage III or stage II disease were advised only supportive care. However, some patients with stage II disease who had severe pain or bleeding were offered palliative radiation. All patients with stage I disease were treated with a curative intent, either by WLE with or without adjuvant radiation (RT) or by APR. The decision to proceed with APR or WLE was based on the size and depth of the lesion, assessed by digital rectal examination. Patients with disease involving more than one-fourth of the circumference of the anorectum or those with lesions clinically assessed to be tethered or fixed were offered APR. All the others underwent WLE.

Total mesorectal excision was performed in patients who underwent APR. Patients undergoing WLE were positioned in a lithotomy position. A one in 100,000 solution of adrenaline was injected in the intersphincteric plane through the perianal skin over the intersphincteric groove. Following anal dilation, a Park's anal retractor was inserted to expose the lesion. The margins of resection were marked out on the mucosa with diathermy, giving a clearance of 1 cm. The incision was deepened to the intersphincteric plane, in which the dissection was carried out. After the specimen was removed, the clearance in the third dimension (internal sphincter) was ascertained. If the tumor was found to come out through the internal sphincter, an APR would be carried out. External beam RT was delivered in conventional fractions (200 cGy/day) using a four field box technique to a total dose range of 50-60 Gy in the adjuvant sitting and 30-40 Gy in the palliative group. Three patients received adjuvant chemotherapy with dacarbazine and melphalan, the indication for which was not mentioned clearly in the records.

All patients were followed-up until death or till the time of this analysis. The actual survival of these patients has been calculated from the date of completion of their treatment. Survival was correlated with clinical and pathological factors and the method of treatment. Tests

for statistical significance could not be done due to the small number of cases.

Results

Clinical features and treatment

Among the 63 patients evaluated, 11 had stage I disease (18%), 16 had stage II disease (25%) and 36 had stage III disease (57%). Ten patients with stage II disease had only inguinal nodal metastasis, whereas two had only iliac nodes and four had both inguinal and iliac nodes. The inguinal nodal disease was unilateral in five patients and bilateral in nine. Among the stage III patients, 18 had metastasis in the liver, 12 in the lung and six had both liver and lung metastasis.

Clinical details of all the 63 patients are enumerated in Table 1. Out of the 63 patients, only 18 were treated- 11 (stage I) by surgery and seven (stage II) by radiation alone. The surgical procedure included WLE in eight and APR in three patients [Table 2].

Two patients were referred to our Institution after undergoing wide local excision elsewhere, of whom one underwent re-excision for residual disease. On grossing the specimen immediately following WLE, none of the eight patients were found to have disease coming out of

Table 1: Clinicopathological features of 63 patients with anorectal melanoma

Median age (range)	53 years (32-79 years)
Male:Female (number)	34:29
Stage (number)	
I	11
II	16
III	36
Symptoms	
Bleeding per rectum	83%
Mass in rectum	25%
Pain	17%
Altered bowel habits	17%
Median size (range)	3cm (1.8-10 cm)
Location* (number)	
Below dentate line	20
At the dentate line	12
Above dentate line	6
Not known [†]	25

*Refers to the epicentre of the lesion

[†]Epicentre cannot be identified due to the large size of the lesion

Table 2: Details of the 11 patients treated by surgery

Age/Sex	Location* (cm)	IHC done	Size (cm)	Depth	Treatment	Resection margin (cm)	Adjuvant chemo	OS (months)	Site of recurrence
71/M	1	Yes	3	SM	WLE	0.9	No	7	L, D
48/M	4	Yes	1.8	M	WLE	1	No	64	L
52/M	2	No	2	M	WLE	1.3	Yes	240	L [†]
45/F	1	No	2.2	SM	WLE	1.2	Yes	12	D
46/M	3	No	2.5	MP	WLE	1.2	No	11	L, R
48/M	2.5	No	3	NA	WLE + RT	NA	Yes	9	D
38/M	2	Yes	2	M	WLE + RT	1.2	No	102	Nil
57/M	3	Yes	3	SM	WLE + RT	1	No	34	D
60/M	1.5	Yes	5	MP	APR	1 [†]	No	8	R, D
35/M	1	Yes	4.2	PR	APR	1 [†]	No	12	Nil
48/F	0	Yes	5	PR	APR	1 [†]	No	11	R, D

*Distance from anal verge

[†]All patients who underwent APR had distal resected margins of at least 1 cm. Minimal circumferential margin was 5mm

[‡]Local recurrence was salvaged

M - mucosa, SM - submucosa, MP - muscularis propria, PR - perirectal tissue, L - local, R - regional, D - distant, NA - not available, OS - overall survival

Patients 5 and 6 were referred after excision. Patient 5 underwent re-excision of residual disease

the internal sphincter, and hence, none of them needed conversion to APR. In all these eight patients, part of the circumference of the internal sphincter and the entire external sphincter complex was preserved.

Adjuvant external beam radiation to the pelvis and inguinal regions was recommended in two patients who were referred to us after a WLE elsewhere, while the reason for giving adjuvant brachytherapy in one patient could not be ascertained from the records.

Pathological features

The depth of infiltration of the lesion could be ascertained in ten out of 11 patients who underwent surgery [Table 2]. In one patient who was referred to us after excision, details of depth and resection margins could not be obtained. The seven patients who received palliative RT had clinically fixed tumors that had obviously involved the muscularis propria or deeper layers. Information on the tumor thickness was not available for any of the patients. Immunohistochemical studies were done in only nine of the 18 treated patients, and positive staining for Vimentin, Keratin, S-100 and HMB-45 was detected in 78%, 23%, 78% and 89% of these patients respectively [Figure 1]. In the two patients with keratin positivity, both S-100 and HMB-45 were also positive.

Treatment outcome

The median overall survival of patients with stage I,

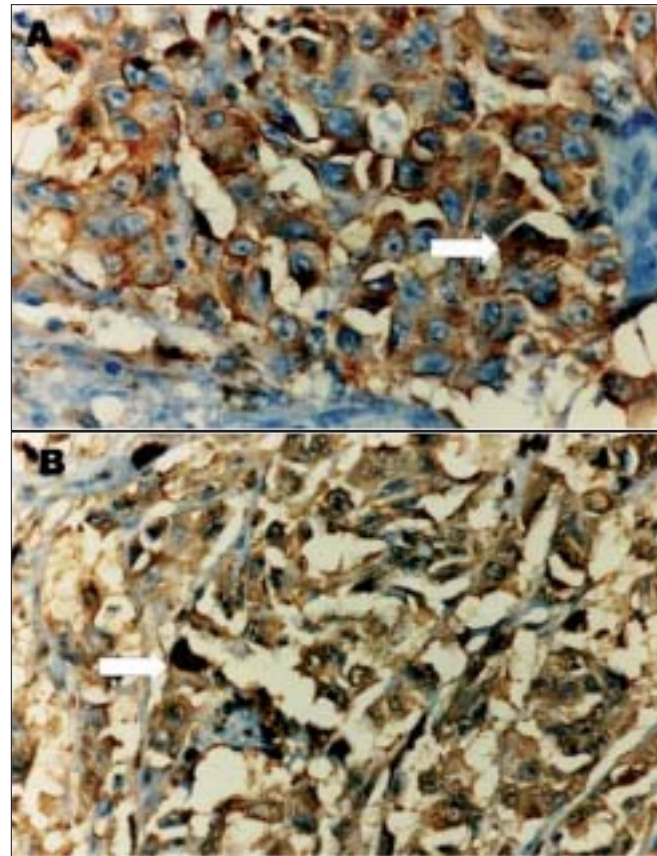


Figure 1: Immunohistochemical staining (white arrow) in anorectal melanoma: A) S-100p and B) HMB 45 (x10)

Table 3: Treatment outcome

Treatment	No. of patients	Median overall survival (months)	Median disease free survival (months)	Current status		
				Dead	AWD	ADF
WLE	5	12	8	3	1	1
WLE + RT	3	34	28	2	Nil	1
Abdominoperineal resection	3	10	5	2	Nil	1
RT only	7	4	0	7	Nil	Nil

ADF - Alive and disease free, AWD - Alive with disease

Table 4: Recurrence patterns following treatment*

Treatment	Total no.	Local recurrence		Nodal recurrence	Distant recurrence
		Total	Isolated		
WLE	5	4	2	2	2
WLE + RT	3	Nil	Nil	Nil	2
APR	3	Nil	Nil	2	2

*Combination of sites is possible

stage II and stage III disease was twelve, seven and four months (range 7 to 240, 5 to 12 and 2 to 7 months) respectively. Median overall survival in the 18 treated patients was 9.5 months (range 3 to 240) and median disease free survival was seven months (range 0 to 180). Patients treated with WLE and adjuvant RT had a trend towards better survival than those treated by either APR or WLE alone [Table 3]. Of the seven patients who received palliative radiation, three had partial regression of the tumor with satisfactory palliation (one of whom survived for more than a year), while the remaining four had progressive disease.

Local recurrence following surgery was observed in four of the five patients treated by WLE alone. However, 50% of these patients had associated nodal or distant metastasis as well [Table 4]. Though none of the three patients treated by APR had a local recurrence, two had a nodal recurrence in the inguinal and iliac regions. None of the patients who received RT following WLE had a local or nodal recurrence. Distant metastasis developed in six of the 11 patients treated by surgery within a median interval of seven months.

Three of the eighteen patients have survived beyond five years [Table 2]. The first was a 48-year-old male who underwent WLE of a polypoidal lesion. After three years of follow-up, he defaulted and later presented with a large local recurrence after two years for which he was advised an APR, but he refused. The second patient was

a 52-year-old man who underwent WLE of a 1.8 cm tumor located 3 cm from the anal verge, followed by two cycles of melphalan. After 15 years of the initial surgery, he developed a recurrence in the anal canal adjacent to the site of previous excision. This lesion was also excised with negative margins and was again pathologically confined only to the mucosa. He is alive and disease-free five years after the second surgery. The third patient received adjuvant RT following WLE of a lesion 2 cm in size. He is alive without disease 8.5 years after treatment. Interestingly, all these three patients had a tumor less than or equal to 2 cm in size, all had disease confined to the mucosa and all had margins of resection of at least 1 cm.

Prognostic factors

We attempted to analyze the prognostic factors only in the 11 patients who underwent surgery. The factors studied were the size, depth of invasion, mode of treatment and duration of symptoms. Patients with a tumor size ≤ 2 cm had a better median survival (102 months) than those with tumors more than 2 cm in size (11.5 months). The median survival of patients in whom the disease was confined to the mucosa was 102 months, while it was 11 months in those with tumor infiltration into the submucosa or beyond. The only site of recurrence in patients with mucosa confined disease was local, whereas patients with disease beyond the mucosa had a nodal or distant recurrence also [Table 2]. Patients who underwent WLE with RT had a longer survival than the other treatment groups [Table 3]. The median survival in patients in whom the duration of symptoms was less than three months or more than three months was 10 and 12 months respectively. However, the small numbers make any meaningful analysis for prognostic factors difficult.

All the patients who underwent WLE, including those who received adjuvant RT had satisfactory continence. Complications of radiation in the three patients who received adjuvant RT included radiation induced dermatitis of the groin folds (grade 2 in one

patient and grade 1 in another) and grade 1 proctitis in two patients.

Discussion

Anorectal melanoma is a very rare malignancy. Between 1984 and 1998, these tumors accounted for 1.5% and 2.8% of all anorectal malignancies registered at the population based Madras Metropolitan Tumor Registry^[12] and the hospital based cancer registry of our institution respectively. The increase in the number of cases in our hospital compared to the general population may be due to a referral bias. Though the incidence of carcinoma of the anorectal region in India is low when compared to the western countries,^[13] the incidence of anorectal melanoma in India seems to be higher than that reported in western literature. Although the sex distribution among the 63 patients was comparable (M:F = 34:29), stage I disease was more common in males compared to females (M:F = 9:2). In nine out of 63 patients, IHC studies were required to label a poorly differentiated tumor of the anorectum as a melanoma. Since melanin pigments may be present only in 71 to 88% of cases,^[5,6,14] IHC studies are useful in categorizing poorly differentiated neoplasms of the anal canal.^[14]

Historically, the primary mode of treatment for anorectal melanoma has always been surgery. In the absence of randomized studies, there exists conflicting reports in literature regarding the optimal surgical procedure. The rationale for APR or WLE has been summarized previously.^[9,10] Though local control rates following APR is far superior to that achieved with WLE, APR has not been found to confer any survival advantage when compared to WLE [Table 5]. In one series, however, local excision resulted in better local control than APR, though this may be partly due to the use of adjuvant RT in some patients who underwent WLE.^[11] The apparent improvement in survival of patients treated with WLE and adjuvant RT in our series may be due to the fact that a higher percentage of patients in this

group had early stage disease (confined to the mucosa) and smaller tumors as compared to the patients treated by APR.

Droesch *et al.*^[8] reviewed 14 studies of anorectal melanoma comprising 301 treated patients and found that although the overall median survival of patients treated with WLE or APR was not significantly different, the median survival in stage I patients treated with WLE was significantly superior to those undergoing APR (44 vs 22 months; $P = 0.001$). The current trend therefore, is to do a WLE wherever possible.^[4,8,9,11,15] The recommended margins for excision is 1 cm,^[1,4] though one author has suggested guidelines for management of anal melanoma based on tumor thickness.^[15] Our resection includes the underlying internal sphincter. As long as the anorectal bundle and the external sphincters are intact, patients will remain continent, as has been the case in all our patients who underwent WLE.

Melanomas were previously known to be radio resistant. This was attributed to the ability of melanoma cells to repair sublethal and potentially lethal radiation damages.^[17] However, there is now adequate evidence to show that melanoma cells are radiosensitive.^[18] The use of adjuvant RT in mucosal melanoma has also increased.^[2] Postoperative radiation therapy has been shown to improve locoregional control in head and neck mucosal melanoma^[19,20] and female genital melanoma.^[20] In anorectal melanoma, however, adjuvant radiotherapy has been used very sparingly.^[4,9,11,21]

The radiation fractionation schedule for treatment of melanoma is controversial. Schedules using high dose per fraction has been shown to overcome the repair of sublethal damage in patients with melanoma.^[22] The use of hypofractionated radiotherapy has been associated with better response rates as compared to conventional fractionation in some series.^[17,22] Ballo *et al.* used adjuvant hypofractionated radiation following local excision in 23 patients with anorectal melanoma

Table 5: Local recurrence and survival - abdominoperineal resection vs wide local excision

Author	Year	No. of pts		Stage	Median OS (months)		Local recurrence	
		APR	WLE		APR	WLE	APR	WLE
Pessaux ^[10]	2004	21	9	I,II	33%*	16%*	22%	48%
Bullard ^[11]	2003	4	11	I,II	14	19	50%	18%
Weyandt ^[15]	2003	5	8	I	NA	NA	20%	63%
Moozar ^[16]	2003	4	10	I,II,III	12	6	0%	60%
Our series	2006	3	5	I	10	12	0%	80%

*5-yr overall survival, APR - Abdominoperineal resection, WLE - Wide local excision

to achieve local and regional control rates of 74% and 84% respectively.^[9] Their local control rates are comparable to those reported following APR and superior to those following WLE alone in various series. However, a prospective randomized study, the RTOG 83-05,^[23] that compared the use of large dose per fraction and conventional fractions in treating malignant melanoma did not find any difference in the response rates between the two (24.2% vs 23.4% complete response respectively). The conclusion of this study was that the choice of fractionation should depend on the location, convenience, life expectancy and efficacy. Fenig *et al.*^[24] studied the use of adjuvant radiation in cutaneous melanoma and found no advantage of large fractions over conventional fractions (local control rate 82% vs 87% respectively). We have used conventional fractionation routinely for treatment of carcinoma of the anal canal and rectum in a large number of patients and we have found this schedule convenient as well as safe. Hence we follow this schedule in the adjuvant therapy of anorectal melanoma as well.

The most important prognostic indicators in anorectal melanoma include stage of disease,^[8-10] size,^[5] duration of symptoms,^[11] nodal involvement^[2,8-10] and molecular markers like PCNA and Ki-67.^[25] Even though the thickness of the tumor has been found to be a prognostic factor in some studies,^[7,14] Bullard noted that thickness did not correlate with pattern of recurrence or survival.^[11] Also, thickness of the lesion does not always correlate with depth of invasion as thick lesions may be confined to the submucosa while thin ones may invade the muscularis propria.^[26] Invasion into the submucosa gives the tumor cells access to lymphovascular channels, which help in dissemination of the tumor. In our experience, tumor invasion into the submucosa or beyond was associated with increased nodal or distant recurrence and a poor survival, though the statistical significance of this observation could not be determined due to the small study size. In a series from the Mayo Clinic, 80% of patients in whom the tumor had invaded into the submucosa or beyond developed a recurrence, compared to only 50% of patients with tumour confined to the mucosa.^[1] Therefore, we believe that unlike in cutaneous melanoma, it is the invasion into the submucosa or deeper layers rather than the Breslow's thickness that determines the propensity for nodal or distant spread and ultimately, the survival in anorectal melanoma.

Systemic therapy in anorectal melanoma has generally been disappointing, though biochemotherapy has been shown to produce impressive response rates in a metastatic setting.^[27] Unless more effective systemic therapy is developed, the prognosis of patients with

anorectal melanoma will remain poor.

In our experience, as well as that of others,^[4,9] the type of surgery does not alter the natural history of this disease. Therefore, our policy has been to try and achieve maximum local control while minimizing the need for a colostomy. In our experience, the use of adjuvant radiation seems to hold promise in achieving good locoregional control in anorectal melanoma. However, a larger patient database is required to further evaluate the role of adjuvant radiation, which will only be possible by a multi-centre study, given the rarity of this disease. Till then, the local treatment of anorectal melanoma should be individualized for each patient. WLE alone is associated with a high incidence of local recurrence, and hence WLE with adjuvant radiation may be considered in selected patients with small superficial tumors which are suitable for local excision. Use of EUS^[11] or MRI may help in identifying this group of patients. However, an APR should be offered for all advanced, deeply infiltrating lesions where WLE is not possible or as a salvage following local recurrence.

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