Anorectal Malignant Melanoma—Defining the Optimal Surgical Treatment and Prognostic Factors

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Received: 11 December 2017 / Accepted: 13 July 2018 / Published online: 23 July 2018
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Abstract

Patients with anorectal malignant melanoma (ARMM) have a poor prognosis. Optimal surgical treatment is not defined. The aim of the study was to define the surgical treatment for ARMM, to compare the overall survival (OS) of abdomino-perineal resection (APR) and wide local excision (WLE) and to study various prognostic factors. Thirty patients of ARMM were managed, 20 with locoregional disease, 10 metastatic. Of the 20 patients with locoregional disease, 15 underwent APR and 5 WLE. The 1-, 2-, 3-, and 4-year overall survival rates (by Kaplan–Meier survival analysis) in the APR group were 67, 40, 40, and 32%, and in WLE group were 100, 100, 67, and 67% respectively. Median survival for APR and WLE groups were 13 and 36 months and were not significant (p 0.48). Node-negative patients had better survival than node positive in the APR group (56 vs. 13 months) (p 0.017). Patients with tumor size < 2cm, lymphovascular invasion and perineural invasion negative, and margin-negative and with superficial infiltration had a trend toward better survival than their counterparts. WLE gives an equivalent oncological outcome and can be offered for patients with smaller ARMM and APR for locally advanced, larger tumors or as a salvage following recurrence after WLE.

Keywords Anorectal malignant melanoma · Abdomino-perineal resection · Wide local excision · Survival

Background

Malignant melanoma of the anorectal region is a rare and aggressive tumor. It contributes to less than 3% of all malignant melanomas and less than 1% of all anal canal tumors [1]. Surgery is the cornerstone of treatment, and

adjuvant therapy role is unproven. Despite this, the most appropriate surgery remains questionable. The rarity of disease adds to the lack of prospective studies. The prognosis of anorectal melanoma remains poor. The 5-year overall survival rate is generally less than 20%. We present the data of patients with anorectal melanoma who were

Synopsis—WLE gives equivalent oncological outcomes and can be offered for patients with small ARMM and APR for locally advanced, larger tumors or as a salvage following recurrence after WLE.

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managed at our hospital which is a tertiary cancer care center and a teaching hospital.

Material and Methods

From January 2010 to December 2015, records of all patients with malignant melanoma of anal canal and lower rectum who presented to our hospital were searched from a prospectively maintained database. Case records of these patients were retrospectively reviewed to obtain information regarding clinical and pathological features, treatment and follow-up details. All patients were followed until June 2017. Those patients who missed the scheduled follow-up were contacted on telephone until the said date. Under general anesthesia, the digital rectal examination was done to assess the site, size, extent, and mobility of the lesion. Patients with small, polypoidal tumors were offered wide local excision. Patients underwent wide local excision with 1-cm margin all around. The deeper plane was dissected until perirectal fat plane. Margin status of the patients undergoing wide excision was confirmed intraoperatively on frozen section analysis. Patients whose margin status was positive on frozen section analysis or preservation of anal sphincter was not possible were offered abdomino-perineal resection. Also, patients with larger, bulkier tumor or with involved sphincter were offered APR. Median follow-up in the group undergoing curative surgery was 27.5 months (range 20 to 90 months).

Numerical data are presented as mean, median, and frequency wherever appropriate. Numerical data was compared using unpaired *t* test. Kruskal–Wallis one-way analysis of variance by ranks: the test was used for comparing > 2 independent samples. A *p* value of ≤ 0.05 was considered statistically significant. Statistical analyses were done on Graph Prism software version 5 for windows. Survival analysis was done by Kaplan–Meier survival estimates using SPSS 20 software. This study was approved by ethics committee of Basavatarakam Indo American Cancer Hospital and Research Institute, Hyderabad, India.

Results A total of 30 patients had anorectal melanoma. For the purpose of stratification in the present study, patients were classified into stage I (localized disease), stage II (presence of inguinal or pelvic nodes), or stage III (distant metastasis) on the clinical, radiological, and pathological assessment. Ten patients had stage III disease at presentation and the remaining 20 had the locoregional disease. Among them, 9 patients had stage I disease, 11 had stage II.

Twenty patients who had locoregional disease underwent surgery with curative intent. Follow-up after surgery ranged from 20 to 90 months, median follow-up was 27.5 months (WLE 20.0 months; APR 36.0 months).

Mass per anus and bleeding per rectum were the most common presentations. Few patients presented with an altered frequency of motion and perianal pain. The median age of the entire cohort (stage 1 and 2) at presentation was 50 years with equal male and female ratio. The median tumor size was 3 cm. Fifteen patients underwent abdomino-perineal resection and five, wide local excision. Among APR group, 13 underwent laparoscopic APR only, one laparoscopic APR with right inguinal lymph node dissection; another, laparoscopic APR with pelvic lymph node dissection. The median size of the tumor in APR group was 3.5 cm. The details of various demographic parameters are mentioned in Table 1. Median overall survival was 13 months. The survival was significantly poorer in patients with the node-positive disease than node-negative disease i.e., 13 months versus 56 months (*p* 0.017). Eleven patients out of 15 had the pathologically node-positive disease, out of which nine died (81%) and eight died of disease, one died postoperatively due to an acute coronary event. Out of four node-negative patients, three were alive and free of disease and one patient had died of recurrence. Most of the recurrences were systemic and seen in liver, lung, brain, groin and iliac region.

Non-adjusted tumor-related mortality in APR group was 60% (*N* = 9) at the end of median 3 years follow-up. Four APR patients were alive with no evidence of recurrence at a median follow-up of 42 months after the primary procedure. One patient was without any evidence of disease after 90 months after the primary procedure. The overall 1-, 2-, 3-, and 4-year survival rates by Kaplan Meier survival estimates after curative operation in APR group were 67, 40, 40, and 32%, respectively (Fig. 1). Median disease-free survival was 17 months.

Five patients underwent wide local excision. Among these, two patients had excision elsewhere, underwent wide excision at our institute owing to unknown margin status. Details of one patient were not available. The median size of the tumor in wide local excision group was 2 cm (Table 1). All the patients were clinico-radiologically node negative. Median overall survival in the WLE group was 36 months. Two patients had recurrences in the inguinal basin and underwent inguinal block dissection; one was disease free 39 months after inguinal dissection, while another developed two times recurrence in the inguinal region, salvaged by surgery and subsequently died of disease. The overall 1-, 2- 3-, and 4-year survival rates in the WLE group were 100, 100, 67, and 67% respectively by Kaplan–Meier survival estimates. Median disease-free survival was 20 months (Fig. 1).

There was a trend toward better median overall survival in the WLE group than in the APR although not statistically significant, i.e., 36 and 13 months respectively (*p* 0.48).

Fig. 1 Kaplan–Meier survival curves of APR and WLE arms. The upper curve shows WLE arm and lower APR arm

Prognostic factors

Stage was the most important prognostic factor determining survival. The overall survival was significantly better (56 months) in the node-negative patient group than node-positive group (13 months), (comparison was done only in the APR group). Survival was better in patients with tumor size < 2 cm and lymphovascular invasion (LVI)-negative and perineural invasion (PNI)-negative patients when compared to their counterparts but was not significant. Patients with mucosal and submucosal wall infiltration had better survival than those with muscularis propria and perirectal fat infiltration (38 months versus 19 months) although not significant. Patients with the margin-positive disease had a trend toward shorter median overall survival (13 months) than those with margin-negative disease (35 months) (Table 2).

Among the ten patients with metastatic disease, six had metastasis in the liver; others had liver deposits with intestinal obstruction, liver and lung metastases, brain and lung deposits, and non-regional nodes with skeletal metastasis. Two patients underwent palliative APR due to bleeding and pain per rectum. One patient underwent surgery for intestinal obstruction. The median survival of this cohort was 5 months.

DISCUSSION

Malignant melanoma of the anorectum is an aggressive and rare malignancy. Surgery is the mainstay of treatment, and the

role of adjuvant therapies is undefined. Despite this, the most appropriate operation remains controversial. The prognosis of anal melanoma is poor [2]. Many appear without pigmentation, and 20% are truly amelanotic on histologic examination [2] [3]. The presence of melanin pigment in the malignant cells helps in histologic diagnosis. Immunohistochemistry is useful in cases where melanin or junctional changes are absent and the traditional histology is not adequate to make a diagnosis. Melanoma antigens S-100, HMB-45, and vimentin are stained positively in 78, 94, and 100% of tumors [3]. In the present series, immunohistochemical studies were done in 11 out of the 20 patients treated with curative intent.

Patients with anorectal melanoma present with bleeding, anal pain, anal mass, pruritus, tenesmus, and change in bowel habit [2]. The commonest symptom is bleeding which should alarm the evaluation of the entire colon and rectum. There is often delay in diagnosis. Tumors are usually thicker than 1 cm and often ulcerated. In the present series, mass per anus and bleeding per rectum were the most common presentations. Few patients presented with an altered frequency of motion and perianal pain. There is no TNM classification for anorectal melanoma. They are staged clinically based on locoregional spread and distant metastasis. Stage I is the local disease only, stage II is a local disease with regional lymph nodes, and stage III is the distant metastatic disease [2].

The 5-year survival rates are generally less than 20% [1] [4] [5]. The initial stage at presentation determines overall survival [1] [6]. Gender, tumor thickness, and perineural invasion are other prognostic factors [7] [6]. In the present study,

Table 1 Demographic profile of patients in APR and WLE groups

	APR	WLE	<i>p</i> value
Median age (in years)	57	38	0.0313
Sex			1
Male (<i>n</i>)	7	3	
Female (<i>n</i>)	8	2	
Size			0.0726
< 2 cm (<i>n</i>)	3	2	
> 2 cm (<i>n</i>)	12	2	
Depth of infiltration			0.1867
Mucosa (<i>n</i>)	0	1	
Submucosa (<i>n</i>)	2	1	
Muscularis propria (<i>n</i>)	8	2	
Perirectal fat (<i>n</i>)	5	0	
Margins			0.5395
Free (<i>n</i>)	12	5	
Positive (<i>n</i>)	3	0	
Nodes			
Negative (<i>n</i>)	4		
Positive (<i>n</i>)	11		
Perineural invasion			0.5304
Negative (<i>n</i>)	11	4	
Positive (<i>n</i>)	4	0	
Lymphovascular invasion			0.5304
Negative (<i>n</i>)	11	4	
Positive (<i>n</i>)	4	0	
Recurrences Local (<i>n</i>)	2	2	0.2487
Distant recurrences (<i>n</i>)	6	0	0.2663

Details of one patient in WLE who underwent primary surgery elsewhere were not known

median survival of cohort treated with curative surgery was 27.5 months. Eleven patients out of 20 died in this follow-up period and 10 died of disease. In this series, we found the presence of positive nodes at the initial presentation profoundly affected survival. Patients in the APR group with the node-positive disease had statistically poorer median survival than node-negative disease i.e., 13 months versus 56 months (*p* 0.017). Survival was better in patients with tumor size < 2cm, lympho-vascular invasion (LVI) negative, perineural invasion (PNI) negative, margin-negative patients and those with superficial invasion (mucosa and submucosa infiltration) when compared to their counterparts but was not significant.

Surgery is the cornerstone treatment of anal melanoma. The majority of patients are diagnosed at an advanced stage and therefore curative surgery is not possible for this subset of patients. Although the radical surgery APR carries the advantage of a wider excision and mesenteric lymphadenectomy, its superiority over wide local excision is never proved.

Table 2 Study of various prognostic factors on overall survival (OS) in 19 patients

	Median OS in months	<i>p</i> value
Depth of infiltration		0.6471
Mucosa and Submucosa	38	
Muscularis propria and perirectal fat	19	
Nodal status (APR arm only)		0.0173
Positive (<i>n</i> = 11)	13	
Negative (<i>n</i> = 4)	56	
Size		0.6041
≤ 2 cm (<i>n</i> = 5)	24	
> 2 cm (<i>n</i> = 14)	27.5	
Perineural invasion		0.2381
Negative (<i>n</i> = 15)	35	
Positive (<i>n</i> = 4)	9	
Lymphovascular invasion		0.2381
Negative (<i>n</i> = 15)	35	
Positive (<i>n</i> = 4)	11	
Margin		0.2314
Negative (<i>n</i> = 16)	35	
Positive (<i>n</i> = 3)	13	

Details of one patient in WLE arm who underwent resection elsewhere were not known

WLE gives an equivalent oncological outcome with less morbidity and avoids a permanent colostomy. The type of surgical excision is unlikely to influence the pattern of recurrence as anorectal melanoma tend to relapse early and systemically. Traditionally radical surgery APR was considered as an adequate surgery for a good locoregional control, but the experience was limited to small series. Subsequent large series reported equivalent oncological outcomes for WLE comparable to APR with better quality of life post-surgery [2]. Most series have shown good locoregional control rates and a trend toward improved survival in patients undergoing APR than those undergoing WLE. But in the present series, patients in APR group had inferior survival, i.e., 13 months versus 36 months in WLE group though not significant. This discrepancy is due to more advanced, bigger tumor size and node-positive patients underwent APR as against in the WLE group where smaller, superficial tumors and node-negative patients were present. Though few WLE group patients had the locoregional failure, they were successfully salvaged by surgery.

A meta-analysis of 31 studies and 1006 patients of anorectal melanoma showed that overall survival and relapse-free survival did not differ significantly between the APR and WLE groups [8]. APR significantly had reduced local recurrences compared to WLE. This meta-analysis suggested that APR has no survival benefit but

offered a better local control than WLE. Local failures after WLE could be successfully managed by salvage surgery thereby minimizing morbidity and maximizing the quality of life, should be the focus in the surgical treatment of anorectal malignant melanoma ARMM [8]. Kiran et al. analyzed 109 patients with anorectal melanoma from 1982 to 2002 from the Surveillance, Epidemiology and End Results database. Fifty-five percent of patients underwent local resection and 45% radical surgery i.e., APR. Survival was similar after local excision or radical resection irrespective of the localized or regional stage of disease [9]. Nilsson and Ragnarsson-Olding also retrospectively reviewed 251 patients with anorectal melanoma identified between 1960 and 1999 from the Swedish National Cancer Registry. APR and local excision was performed in 66 and 86 patients respectively. Median survival after surgery was similar between wide local excision and APR groups. Patients in whom an R0 resection was achieved, irrespective of approach, had a significantly better overall 5-year survival rate than patients with involved margins [10]. Ross et al. from the M. D. Anderson Cancer Center reviewed a series of 32 patients with melanoma treated with either APR or local resection. Local recurrences occurred less frequently in the APR group than the local excision group (29% for APR; 58% for local excision). There was no difference in overall survival between the two surgically treated groups (19.5 months for APR; 18.9 months for local resection) [11].

CONCLUSIONS

The treatment of anal canal melanoma should be individualized. For an early and superficial disease with a smaller sized lesion, wide local excision seem to be a better option with equivalent oncological outcomes, survival, less morbidity and better functional outcomes and avoids a permanent stoma. The morbid procedure like APR has to be offered to the bulky tumor where WLE cannot be accomplished. The presence of nodal disease is the single most important factor affecting survival. Positive margins, the presence of LVI, PNI, and deeper infiltration portends poor survival but was not significant in the present study. Whenever recurrence occurs in the nodal basin, every effort has to be made to resect as some of these patients can be long-term survivors.

Compliance with Ethical Standards

This study was approved by ethics committee of Basavarakam Indo American Cancer Hospital and Research Institute, Hyderabad, India.

Conflict of Interest The authors declare that they have no conflicts of interest.

Abbreviations ARMM, anorectal malignant melanoma; OS, overall survival; APR, abdomino-perineal resection; WLE, wide local excision; LVI, lymphovascular invasion; PNI, perineural invasion

References

1. Chang AE, Karnell LH, Menck HR (1998) The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer* 83(8):1664–1678
2. Singer M, Mutch MG (2006) Anal Melanoma. *Clin Colon Rectal Surg* 19:78–87
3. Ben-Izhak O, Bar-Chana M, Sussman L, Dobiner V, Sandbank J, Cagnano M, Cohen H, Sabo E (2002) Ki67 antigen and PCNA proliferation markers predict survival in anorectal malignant melanoma. *Histopathology* 41:519–525
4. Brady MS, Kavolius JP, Quan SH (1995) Anorectal melanoma: a 64-year experience at Memorial Sloan-Kettering Cancer Center. *Dis Colon Rectum* 38(2):146–151
5. Whooley BP, Shaw P, Astrow AB et al (1998) Long-term survival after locally aggressive anorectal melanoma. *Am Surg* 64(3):245–251
6. Podnos YD, Tsai NC, Smith D et al (2006) Factors affecting survival in patients with anal melanoma. *Am Surg* 72(10):917–920
7. Weyandt GH, Eggert AO, Houf M et al (2003) Anorectal melanoma: surgical management guidelines according to tumour thickness. *Br J Cancer* 89(11):2019–2022
8. Matsuda A, Miyashita M, Matsumoto S et al (2015) Abdominoperineal resection provides better local control but equivalent overall survival to local excision of anorectal malignant melanoma: a systematic review. *Ann Surg* 261(4):670–677
9. Kiran RP, Rottoli M, Pokala N et al (2010) Long-term outcomes after local excision and radical surgery for anal melanoma: data from a population database. *Dis Colon Rectum* 53(4):402–408
10. Nilsson PJ, Ragnarsson-Olding BK (2010) Importance of clear resection margins in anorectal malignant melanoma. *Br J Surg* 97(1):98–103
11. Ross M, Pezzi C, Pezzi T et al (1990) Patterns of failure in anorectal melanoma: a guide to surgical therapy. *Arch Surg* 125(3):313–316