Review

Primary Anorectal Melanoma: An Update

P Carcoforo[1], M.T Raiji[2], G.M Palini[3], M Pedriali[1], U Maestroni[4], G Soliani[1], A Detroia[1], M.V Zanzi[1], A.L Manna[1], J.G Crompton[5], R.C Langan[2], A Stojadinovic, I Avital[6]✉

1. Section of General Surgery, Department of Surgical, Anaesthesiological and Radiological Sciences, University of Ferrara, Ferrara, Italy;
2. Department of General Surgery, Georgetown University Hospital, Washington DC;
3. Section of Pathology, Department of Experimental and Diagnostic Medicine, University of Ferrara, Ferrara Italy;
4. Department of Surgery, University Hospital of Parma, Parma Italy;
5. Department of Surgery, UCLA Medical Center, Los Angeles CA;
6. Department of Surgery, Division of Surgical Oncology, Walter Reed National Military Medical Center, Bethesda, MD; Bon Secours National Cancer Institute, Richmond VA, USA.

✉ Corresponding author: itzhakavital@gmail.com

Abstract

The anorectum is a rare anatomic location for primary melanoma. Mucosal melanoma is a distinct biological and clinical entity from the more common cutaneous melanoma. It portrays worse prognosis than cutaneous melanoma, with distant metastases being the overwhelming cause of morbidity and mortality. Surgery is the treatment of choice, but significant controversy exists over the extent of surgical resection. We present an update on the state of the art of anorectal mucosal melanoma. To illustrate the multimodality approach to anorectal melanoma, we present a typical patient.

Key words: anorectal mucosal melanoma

Introduction

Malignant melanoma accounts for under 5% of all cases of cutaneous malignancies in the United States, with an annual incidence of approximately 70,000 [1]. However, melanoma is the most fatal skin malignancy, with an annual mortality approaching 10,000. The vast majority of cases of melanoma arise in the skin, while primary melanoma arising from mucosal surfaces occurs in under 2% of cases [2]. Primary mucosal melanoma (MM) is slightly more predominant in females, largely due vulvovaginal melanoma [3]. The distribution of MM involves the head and neck in 55.4% of cases, the anorectum in 23.8%, the female genital tract in 18.0%, and the urinary tract in 2.9% [2]. The diagnosis of anorectal mucosal melanoma (ARMM) portends a particular poor prognosis [4], and a standardized evidence based treatment ap-

proach is not well defined due to the rarity of this disease [5]. Herein, we use a typical patient along with relevant literature to illustrate the multimodality approach to ARMM, and discuss important factors associated with the treatment and prognosis of ARMM.

Typical presentation of anorectal mucosal melanoma

To illustrate a typical presentation of ARMM and its accompanying multimodality approach, we present a 76-year old female presented with a 2-month history of intermittent blood per rectum and tenesmus. On digital rectal examination, a palpable mass at 4 o'clock was noted approximately 2 cm proximal to the anal verge. Rigid proctoscopy demonstrated a 3 cm ulcerated lesion along the dentate line. Multiple

biopsies were taken, and pathologic results were consistent with malignant melanoma. Endoscopic ultrasound demonstrated a 2.5 X 3.5 X 3cm mass with no pathologic lymph nodes visualized. A staging positron emission tomography (PET) scan with computed tomography (CT) was performed, with no evidence of distant metastases.

The patient underwent wide local excision of the primary lesion, preceded by a sentinel lymph node (SLN) mapping with a submucosal injection of 99mTC-Nanocoll. A single pre-sacral SLN was found and biopsied.

The final pathology from the resection specimen demonstrated spindle-shaped, melanotic cells invading into the muscularis propria. The cells demonstrated a high mitotic index, with evidence of vascular invasion. Immunohistochemical (IHC) staining showed strongly positive staining with HMB-45, MART-1, and S100. Additionally, the SLN was found to harbor micrometastases.

Subsequently, the patient received adjuvant chemo-radiation therapy with three cycles of radiation to the surgical site and three cycles of temozolomide. During routine follow-up imaging six months post-procedure, the patient was found to have metastatic deposits in the mesorectal lymph nodes, along with the liver and lung. Fourteen months later, the patient developed rectal bleeding and obstructive symptoms, and was found to have local recurrence in the rectum. A repeat wide local excision was performed, along with a diverting colostomy.

Discussion

Malignant melanoma is the fifth leading cause of new cancer diagnosis in males in the United States, and the sixth in females [6]. This incidence is rising by approximately 3% per year [7], especially among young adults [8]. These increases may be attributed to increased screening and codification of pathologic standards for diagnosis [9]. MM is a rare type of malignant melanoma, and widely considered to be a distinct clinical entity from CM based on its poor prognosis [10]. Though mucosal melanoma arising from various head and neck mucosal surfaces comprises over 50% of MM, the anorectum is a common anatomical site of MM, and is the third most common location for malignant melanoma after cutaneous melanoma (CM) and ocular melanoma [2, 3, 11]. ARMM is also a distinctly rare tumor of the anal canal, comprising less than 4% of malignancies in that region [12].

Considerable dispute exists regarding the cell of origin for ARMM. While the presence of melanocytes has been relatively well described in the mucosa of the head and neck [13, 14] and the esophagus [15, 16], its presence in the intestinal mucosa from the stomach to distal rectum is controversial [17]. Historically, melanocytes have been found within the transition zone beneath the dentate line and increases in number distally toward the anoderm [18, 19]. This has led to the presumption that anorectal melanoma arises from normal melanocytes distal to the dentate line that extend proximally into the rectum [20]. Staining for melanoma markers using various techniques for HMB-45 and S100 have demonstrated that melanocytes present rarely in the mucosal epithelium above the dentate line in normal patients [21]. Additionally, a proliferation of normal melanocytes within the colorectal epithelium proximal to the dentate line has been seen in patients with melanoma arising within the proximal anal canal [21, 22]. This has led to the conclusion that ARMM can arise directly from melanocytes located in the intestinal epithelium of the proximal anus or distant rectum hence, primary anorectal melanoma [23].

Embryologically, cells migrating from the neural crest that enter the dorsolateral pathway differentiate into melanocytes that eventually populate their eventual sites of colonization, while cells entering the ventral pathway are the neurogenic precursors of the peripheral and enteric nervous system [24]. Neural crest cells are typified by a characteristic set of transcription factors including *Snail2 (Slug), Sox10, FoxD3, and* Sox9 [25]. Melanocyte migration and differentiation involves a complex interplay of cell signaling pathways [26]. Specific mutations in the *c-Kit/stem cell factor (SCF)* pathway, the *endothelin receptor type B/endothelin* pathway, and the *Sox10* transcription factor pathway being associated with a variety of related pigment and enteric nervous system disorders including piebaldism, Waardenburg syndrome, and Hirschprung's disease [27-32].

Exposure to ultraviolet (UV) rays, especially UV-B rays at a wavelength of 290 to 320 nm, is clearest risk factor for the development of cutaneous malignancies, including melanoma [33, 34]. While cumulative exposure increases the risk of the more common basal cell (BCC) and squamous cell carcinomas (SCC) of the skin, CM is associated with intense, intermittent exposure to UV rays [35]. Two well described nucleic acid lesions caused by UV-B include 6-4 photoproducts (6-4PP) and cyclobutane pyramidine dimers (CPD) [36]. Accumulation of these signature mutations are seen in BCC and SCC, including *p16/INK4A and p53* [37]. Mutations in *BRAF* is the most common driver mutation in malignant melanoma, found in upwards of 60% of all CMs and 80% of melanocytic nevi, the vast majority being the V600E amino acid

substitution at exon 15 [38-40]. While the signature UV-associated 6-4PP and CPD nucleic acid mutations are not found to be the etiology of *BRAF* mutations, there is evidence that faulty repair of UV-A associated oxidative damage and other UV-B associated mutations may be the etiology of *BRAF* mutations in CM [41].

The role of photocarcinogenesis in CM is highlighted by the different patterns of mutations associated with MM. Edwards et al evaluated primary MM tumors from varying anatomical locations and found no evidence of *BRAF* mutation, in stark contrast to the prevalence of this mutation in CM [42]. Along with a paucity of *BRAF* mutations [43], similar studies have shown decreased *NRAS* mutations in MM compared to CM [44, 45], while *KIT* driver mutations are increased in MM [46, 47]. Other mechanisms of pathogenesis for MM have been investigated, including viral infections [48] and the use of tobacco [49], but no clear etiology of MM has been elucidated.

Due to its relative rarity, the treatment of ARMM is controversial. While it is clear that surgical resection is favored, the extent of surgery has been called into question as upwards of 25% of patients with ARMM present with inoperable tumors, either because of distant metastases or aggressive locoregional disease [2, 3]. 60% of patients present with local lymphatic spread [2]. This aggressive local disease led to the suggestion that an abdominoperineal resection (APR) be the treatment of choice in order to address local lymph nodes [50-53]. Brady et al reported on 71 patients with ARMM treated with either abdominoperineal resection (APR), wide local excision (WLE), or biopsy and/or fulgration only [54]. While no significant difference in survival was found regardless of operative approach, the local recurrence rate was 8% for APR versus 20% for local therapies.

Given the morbidity of APR and the clear quality of life advantages of WLE [55], there has been persistent concerns regarding an aggressive surgical approach with no clearly demonstrated survival advantage [5, 56]. Iddings et al reported on patterns of treatment and outcomes in patients with ARMM from the SEER database and found no significant different in five-year survival between patients undergoing APR versus WLE (17% and 19%, respectively) [57]. Nilsson et al found that margins of resection significantly predicted long-term advantage, with 5-year survivals of 19% for patients receiving an R0 resection, compared to 6% for patients with R+ resections, regardless of the type of surgery [58]. Of note, patients undergoing APR were significantly more likely to receive an R0 resection (76%) compared to those undergoing WLE (26%). Our patient did undergo WLE,

but notably had an R1 resection, with microscopic involvement of the margins of resection. The role of reoperation for margins after an initial WLE has not been addressed in the literature.

As was the case in our patient, distant metastases areoverwhelmingly the cause of mortality in patients with ARMM, leading to the suggestion that WLE be the initial procedure of choice [59]. However, as demonstrated in our case, patients with local recurrence often require repeat excisions, occasionally including salvage APR [60]. With reports of local recurrence rates as high as 65% with WLE alone [61], investigations into improved local control with the addition of radiation have been undertaken. Kelly et al reported on 54 patients undergoing WLE followed by adjuvant radiation, and showed a local recurrence rate of 18% at 5 years [62].

A lingering question in the treatment of ARMM involves the approach to nodal disease. The use of sentinel lymph node (SLN) mapping has been reported, with subclinical nodal disease found in the inguinal and pelvic nodal basin SLNs [62-66]. No series large enough has been reported to draw conclusions on the effect of SLN biopsy on recurrence or survival, leading some to conclude that the procedure should not be performed [67]. The presence of regional lymph node metastases has not been shown to affect recurrence patterns [4], lending further support to the avoidance of lymphadenectomy. In our patient, with a positive mesorectal SLN, we opted to avoid pelvic exploration as there is no evidence supporting an improved outcome with extended lymphadenectomy.

The preponderance of data suggests that, while extended surgical procedures for ARMM afford no survival benefit, there appears to be significant benefit to achieving an R0 resection. We recommend, based on a review of the literature, the use of intraoperative frozen sections to insure that WLE is performed to negative margins. Reoperative excision of margins may be necessary to render patients disease free and thereby increase the likelihood of cure.

Conclusion

ARMM is a rare malignancy that seems to lack the risk factors associated with cutaneous malignancies. The diagnosis of ARMM portends a poor prognosis, with distant metastases being a common and fatal development. There is a clear advantage to complete R0 surgical excision. While neither surgery nor radiation has had a clear impact on survival, adjuvant radiotherapy does appear to provide greater loco-regional disease control. Due to the rarity of this disease process, no prospective, randomized trials can

definitively elucidate the ideal multimodality therapy for ARMM. Despite this, our retrospective review of the literature leads us to recommend a complete R0 resection for patients with ARMM.

Contributing Author Declaration

We certify that all individuals who qualify as authors have been listed; each has participated in one or more of the following areas: conception and design of this work, the acquisition and/or analysis of data, the writing, and/or critical revision of the document, and supervision of this cooperative research effort. All contributing authors approve of the submission of this version of the manuscript and assert that the document represents valid work. If information derived from another source was used in this manuscript, we obtained all necessary approvals to use it and made appropriate acknowledgements in the document. All contributing authors take public responsibility for this work.

Funding

All authors declare no source of funding.

Disclaimer

The views expressed in this manuscript are those of the authors and do not reflect the official policy of Department of the Army, the Department of Defense or the United States Government.

Copyright protection

Some of the contributing authors are military service members or employees of the U.S. Government, and this work was prepared as part of their official duties. Title 17 U.S.C. 105 provides the "Copyright protection under this title is not available for any work of the United States Government." Title 17 U.S.C. 101 defines a U.S. Government work as a work prepared by a military service member or employee of the U.S. Government as part of that person's official duties.

Competing Interests

The authors have declared that no competing interest exists.

References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011; 61: 212-36. doi:10.3322/caac.20121.
2. Chang AE, Karnell LH, Menck HR. 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. 1998; 83: 1664-78.
3. McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. Cancer. 2005; 103: 1000-7. doi:10.1002/cncr.20866.
4. Thibault C, Sagar P, Nivatvongs S, Ilstrup DM, Wolff BG. Anorectal melanoma--an incurable disease? Dis Colon Rectum. 1997; 40: 661-8.
5. Ross M, Pezzi C, Pezzi T, Meurer D, Hickey R, Balch C. Patterns of failure in anorectal melanoma. A guide to surgical therapy. Arch Surg. 1990; 125: 313-6.
6. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012; 62: 10-29. doi:10.3322/caac.20138.
7. Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the United States. J Invest Dermatol. 2009; 129: 1666-74. doi:10.1038/jid.2008.423.
8. Reed KB, Brewer JD, Lohse CM, Bringe KE, Pruitt CN, Gibson LE. Increasing incidence of melanoma among young adults: an epidemiological study in Olmsted County, Minnesota. Mayo Clin Proc. 2012; 87: 328-34. doi:10.1016/j.mayocp.2012.01.010.
9. Weyers W. The 'epidemic' of melanoma between under- and overdiagnosis. J Cutan Pathol. 2012; 39: 9-16. doi:10.1111/j.1600-0560.2011.01831.x.
10. Tomicic J, Wanebo HJ. Mucosal melanomas. Surg Clin North Am. 2003; 83: 237-52. doi:10.1016/S0039-6109(02)00100-7.
11. Bolivar JC, Harris JW, Branch W, Sherman RT. Melanoma of the anorectal region. Surg Gynecol Obstet. 1982; 154: 337-41.
12. Leonard D, Beddy D, Dozois EJ. Neoplasms of anal canal and perianal skin. Clin Colon Rectal Surg. 2011; 24: 54-63. doi:10.1055/s-0031-1272824.
13. Trodahl JN, Sprague WG. Benign and malignant melanocytic lesions of the oral mucosa. An analysis of 135 cases. Cancer. 1970; 25: 812-23.
14. Rapini RP, Golitz LE, Greer RO, Jr., Krekorian EA, Poulson T. Primary malignant melanoma of the oral cavity. A review of 177 cases. Cancer. 1985; 55: 1543-51.
15. De La Pava S, Nigogosyan G, Pickren JW, Cabrera A. Melanosis of the esophagus. Cancer. 1963; 16: 48-50.
16. Chang F, Deere H. Esophageal melanocytosis morphologic features and review of the literature. Arch Pathol Lab Med. 2006; 130: 552-7. doi:10.1043/1543-2165(2006)130[552:EMMFAR]2.0.CO;2.
17. Piris A, Rosai J. Pigmented lesions in unusual anatomic sites. Semin Diagn Pathol. 2003; 20: 249-59.
18. Walls EW. Observations on the microscopic anatomy of the human anal canal. Br J Surg. 1958; 45: 504-12.
19. Fenger C, Lyon H. Endocrine cells and melanin-containing cells in the anal canal epithelium. Histochem J. 1982; 14: 631-9.
20. Morson BC, Volkstadt H. Malignant melanoma of the anal canal. J Clin Pathol. 1963; 16: 126-32.
21. Clemmensen OJ, Fenger C. Melanocytes in the anal canal epithelium. Histopathology. 1991; 18: 237-41.
22. Werdin C, Limas C, Knodell RG. Primary malignant melanoma of the rectum. Evidence for origination from rectal mucosal melanocytes. Cancer. 1988; 61: 1364-70.
23. Nicholson AG, Cox PM, Marks CG, Cook MG. Primary malignant melanoma of the rectum. Histopathology. 1993; 22: 261-4.
24. Erickson CA. From the crest to the periphery: control of pigment cell migration and lineage segregation. Pigment Cell Res. 1993; 6: 336-47.
25. Bronner ME, Ledouarin NM. Development and evolution of the neural crest: An overview. Dev Biol. 2012; 366: 2-9. doi:10.1016/j.ydbio.2011.12.042.
26. Kawakami A, Fisher DE. Key discoveries in melanocyte development. J Invest Dermatol. 2011; 131: E2-4. doi:10.1038/skinbio.2011.2.
27. Rovasio RA, Faas L, Battiato NL. Insights into Stem Cell Factor chemotactic guidance of neural crest cells revealed by a real-time directionality-based assay. Eur J Cell Biol. 2012; 91: 375-90. doi:10.1016/j.ejcb.2011.12.007.
28. Steel KP, Davidson DR, Jackson IJ. TRP-2/DT, a new early melanoblast marker, shows that steel growth factor (c-kit ligand) is a survival factor. Development. 1992; 115: 1111-9.
29. Bondurand N, Dastot-Le Moal F, Stanchina L, Collot N, Baral V, Marlin S, et al. Deletions at the SOX10 gene locus cause Waardenburg syndrome types 2 and 4. Am J Hum Genet. 2007; 81: 1169-85. doi:10.1086/522090.
30. Pingault V, Bondurand N, Kuhlbrodt K, Goerich DE, Prehu MO, Puliti A, et al. SOX10 mutations in patients with Waardenburg-Hirschsprung disease. Nat Genet. 1998; 18: 171-3. doi:10.1038/ng0298-171.
31. Giebel LB, Spritz RA. Mutation of the KIT (mast/stem cell growth factor receptor) protooncogene in human piebaldism. Proc Natl Acad Sci U S A. 1991; 88: 8696-9.
32. Spritz RA. Piebaldism, Waardenburg syndrome, and related disorders of melanocyte development. Semin Cutan Med Surg. 1997; 16: 15-23.

33. Gilchrest BA, Eller MS, Geller AC, Yaar M. The pathogenesis of melanoma induced by ultraviolet radiation. N Engl J Med. 1999; 340: 1341-8. doi:10.1056/NEJM199904293401707.

34. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005; 41: 45-60. doi:10.1016/j.ejca.2004.10.016.

35. Nelemans PJ, Groenendal H, Kiemeney LA, Rampen FH, Ruiter DJ, Verbeek AL. Effect of intermittent exposure to sunlight on melanoma risk among indoor workers and sun-sensitive individuals. Environ Health Perspect. 1993; 101: 252-5.

36. Jhappan C, Noonan FP, Merlino G. Ultraviolet radiation and cutaneous malignant melanoma. Oncogene. 2003; 22: 3099-112. doi:10.1038/sj.onc.1206450.

37. Pfeifer GP, You YH, Besaratinia A. Mutations induced by ultraviolet light. Mutat Res. 2005; 571: 19-31. doi:10.1016/j.mrfmmm.2004.06.057.

38. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002; 417: 949-54. doi:10.1038/nature00766.

39. Pollock PM, Harper UL, Hansen KS, Yudt LM, Stark M, Robbins CM, et al. High frequency of BRAF mutations in nevi. Nat Genet. 2003; 33: 19-20. doi:10.1038/ng1054.

40. Grossmann AH, Grossmann KF, Wallander ML. Molecular testing in malignant melanoma. Diagn Cytopathol. 2012; 40: 503-10. doi:10.1002/dc.22810.

41. Thomas NE, Berwick M, Cordeiro-Stone M. Could BRAF mutations in melanocytic lesions arise from DNA damage induced by ultraviolet radiation? J Invest Dermatol. 2006; 126: 1693-6. doi:10.1038/sj.jid.5700458.

42. Edwards RH, Ward MR, Wu H, Medina CA, Brose MS, Volpe P, et al. Absence of BRAF mutations in UV-protected mucosal melanomas. J Med Genet. 2004; 41: 270-2.

43. Helmke BM, Mollenhauer J, Herold-Mende C, Benner A, Thome M, Gassler N, et al. BRAF mutations distinguish anorectal from cutaneous melanoma at the molecular level. Gastroenterology. 2004; 127: 1815-20.

44. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005; 353: 2135-47. doi:10.1056/NEJMoa050092.

45. Wong CW, Fan YS, Chan TL, Chan AS, Ho LC, Ma TK, et al. BRAF and NRAS mutations are uncommon in melanomas arising in diverse internal organs. J Clin Pathol. 2005; 58: 640-4. doi:10.1136/jcp.2004.022509.

46. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol. 2006; 24: 4340-6. doi:10.1200/JCO.2006.06.2984.

47. Beadling C, Jacobson-Dunlop E, Hodi FS, Le C, Warrick A, Patterson J, et al. KIT gene mutations and copy number in melanoma subtypes. Clin Cancer Res. 2008; 14: 6821-8. doi:10.1158/1078-0432.CCR-08-0575.

48. Giraud G, Ramqvist T, Ragnarsson-Olding B, Dalianis T. DNA from BK virus and JC virus and from KI, WU, and MC polyomaviruses as well as from simian virus 40 is not detected in non-UV-light-associated primary malignant melanomas of mucous membranes. J Clin Microbiol. 2008; 46: 3595-8. doi:10.1128/JCM.01635-08.

49. Axell T, Hedin CA. Epidemiologic study of excessive oral melanin pigmentation with special reference to the influence of tobacco habits. Scand J Dent Res. 1982; 90: 434-42.

50. Quan SH, Deddish MR. Noncutaneous melanoma. Malignant melanoma of the anorectum. CA Cancer J Clin. 1966; 16: 111-4.

51. Pack GT, Oropeza R. A comparative study of melanoma and epidermoid carcinoma of the anal canal: A review of 20 melanomas and 29 epidermoid carcinomas (1930 to 1965). Dis Colon Rectum. 1967; 10: 161-76.

52. Chiu YS, Unni KK, Beart RW, Jr. Malignant melanoma of the anorectum. Dis Colon Rectum. 1980; 23: 122-4.

53. Slingluff CL, Jr., Vollmer RT, Seigler HF. Anorectal melanoma: clinical characteristics and results of surgical management in twenty-four patients. Surgery. 1990; 107: 1-9.

54. Brady MS, Kavolius JP, Quan SH. Anorectal melanoma. A 64-year experience at Memorial Sloan-Kettering Cancer Center. Dis Colon Rectum. 1995; 38: 146-51.

55. Stoidis CN, Spyropoulos BG, Misiakos EP, Fountzilas CK, Paraskeva PP, Fotiadis CI. Diffuse anorectal melanoma; review of the current diagnostic and treatment aspects based on a case report. World J Surg Oncol. 2009; 7: 64. doi:10.1186/1477-7819-7-64.

56. Wanebo HJ, Woodruff JM, Farr GH, Quan SH. Anorectal melanoma. Cancer. 1981; 47: 1891-900.

57. Iddings DM, Fleisig AJ, Chen SL, Faries MB, Morton DL. Practice patterns and outcomes for anorectal melanoma in the USA, reviewing three decades of treatment: is more extensive surgical resection beneficial in all patients? Ann Surg Oncol. 2010; 17: 40-4. doi:10.1245/s10434-009-0705-0.

58. Nilsson PJ, Ragnarsson-Olding BK. Importance of clear resection margins in anorectal malignant melanoma. Br J Surg. 2010; 97: 98-103. doi:10.1002/bjs.6784.

59. Zhou HT, Zhou ZX, Zhang HZ, Bi JJ, Zhao P. Wide local excision could be considered as the initial treatment of primary anorectal malignant melanoma. Chin Med J (Engl). 2010; 123: 585-8.

60. Moozar KL, Wong CS, Couture J. Anorectal malignant melanoma: treatment with surgery or radiation therapy, or both. Can J Surg. 2003; 46: 345-9.

61. Che X, Zhao DB, Wu YK, Wang CF, Cai JQ, Shao YF, et al. Anorectal malignant melanomas: retrospective experience with surgical management. World J Gastroenterol. 2011; 17: 534-9. doi:10.3748/wjg.v17.i4.534.

62. Kelly P, Zagars GK, Cormier JN, Ross MI, Guadagnolo BA. Sphincter-sparing local excision and hypofractionated radiation therapy for anorectal melanoma: A 20-Year Experience. Cancer. 2011. doi:10.1002/cncr.26088.

63. Damin DC, Rosito MA, Spiro BL. Long-term survival data on sentinel lymph node biopsy in anorectal melanoma. Tech Coloproctol. 2010; 14: 367-8. doi:10.1007/s10151-010-0643-7.

64. Tien HY, McMasters KM, Edwards MJ, Chao C. Sentinel lymph node metastasis in anal melanoma: a case report. Int J Gastrointest Cancer. 2002; 32: 53-6. doi:10.1385/IJGC:32:1:53.

65. Olsha O, Mintz A, Gimon Z, Gold Deutch R, Rabin I, Halevy A, et al. Anal melanoma in the era of sentinel lymph node mapping: a diagnostic and therapeutic challenge. Tech Coloproctol. 2005; 9: 60-2. doi:10.1007/s10151-005-0196-3.

66. Sanli Y, Turkmen C, Kurul S, Tas F, Mudun A, Cantez S. Sentinel lymph node biopsy for the staging of anal melanoma: report of two cases. Ann Nucl Med. 2006; 20: 629-31.

67. Mariolis-Sapsakos T, Malamitsi J, Yakoumakis E, Orfanos F. Is sentinel node mapping useful in anorectal melanoma? Hell J Nucl Med. 2008; 11: 39-42.