**Less is more: a systematic review and meta-analysis of the outcomes of radical versus conservative primary resection in anorectal melanoma.**

Smith HG1,2, Glen J3,4, Turnbull N5, Peach H6, Board R7, Payne M8, Gore M1, Nugent K9, Smith MJF1

1The Skin Unit, The Royal Marsden Hospital NHS Foundation Trust, London, England.

2Digestive Disease Center, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark.

3National Guideline Centre, Royal College of Physicians, London, England.

4The Health Research Council of New Zealand, Auckland, New Zealand.

5Melanoma Focus, London, England.

6Leeds Teaching Hospitals NHS Foundation Trust, UK

7Lancashire Teaching Hospitals NHS Foundation Trust, UK

8Oxford University Hospitals NHS Foundation Trust, UK

9University Hospital Southampton NHS Foundation Trust, UK

**Corresponding author:** Mr M.J.F. Smith, The Skin Unit, The Royal Marsden Hospital NHS Foundation Trust, Fulham Road, London, SW3 6JJ, England.

Email: [myles.smith@rmh.nhs.uk](mailto:myles.smith@rmh.nhs.uk)

**Acknowledgements:** Professor M Gore and Mr MJF Smith and are supported by the NIHR Biomedical Research Centre The Royal Marsden Hospital.

**Conflicts of interest:** None to declare.

**Abstract**

**Introduction:** Anorectal melanoma (ARM) is a rare disease with a poor prognosis. There is no consensus as to the optimal primary surgical treatment for ARM, with advocates for both radical (abdominoperineal resection (APR)), and conservative strategies (wide local excision (WLE)). Here we report a systematic review of studies comparing outcomes between these strategies.

**Methods:** Studies comparing APR with WLE in patients with ARM were included and systematic review using the GRADE methodology was performed. Outcomes deemed critical included overall survival, disease-free survival, local recurrence and quality of life.

**Results:** 40 studies were identified, of which 27 were suitable for inclusion. 23 studies compared overall survival between WLE and APR, with no difference in outcome noted (Risk ratio (RR) 0.80, 95% CI 0.60-1.07, p = 0.13). 7 studies compared disease-free survival, with no difference in outcome noted (RR 1.08, 95% CI 0.61-1.91, p = 0.79). A total of 19 studies compared local recurrence rates, with again no significant difference in outcome noted (RR 0.71, 95% CI 0.44-1.14, p = 0.16). None of the studies identified reported quality of life related outcomes.

**Conclusion:** There is no evidence to suggest a radical primary surgical strategy improves outcomes in ARM. Therefore, given the well-documented morbidity associated with APR, WLE with regular surveillance for local recurrence should be the primary strategy in the majority of patients.

**Introduction**

Anorectal melanoma is a rare and aggressive disease, first described by Moore in 1857 1. Population-based studies report an incidence of 0.3-1.0 per million population, with an increasing frequency in recent years 2-5. Anorectal melanomas are more commonly reported in females and occur with increasing frequency in the elderly 2,3,5-7. Originating from melanocytes in the mucosa of the anorectal junction, approximately 60% of anorectal melanomas occur in the anal canal or at the anal verge, with the remaining 40% occurring within the rectum 2,3,5,8,9. Diagnosis at an advanced stage and delays in diagnosis are not uncommon as these lesions are often mistaken for benign anorectal pathologies, such as haemorrhoids or adenomatous polyps 6,10. Approximately one third of patients present with localised disease, with the potential for curative resection, while the remainder present with synchronous regional or distant metastases 2,6,7,9. Anorectal melanoma is not currently included in TNM staging systems 11. As such an alternative 3 level staging system, as defined by Falch *et al*, is often used, whereby local, regional and disseminated disease are referred to as Stages I, II and III respectively 6. The prognosis for anorectal melanomas is poor, with 5-year survival rates ranging from 5-33% in Stage I disease, with virtually no patients with Stage 3 disease surviving 5 years 6,12.

A common theme encountered in the surgical treatment of anorectal melanoma is the debate regarding the initial operative strategy - whether the approach should be radical, in the form of an abdominoperineal resection, or conservative, in the form of a wide local excision or local mucosal resection. The argument for a radical approach has been the rationale of definitively controlling local disease, as well as locoregional micrometastatic disease and infiltrated lymph nodes, and thereby preventing disease dissemination by removing the source.

However, as has been found in other malignancies, with the archetypal example being breast cancer, radical surgery does not necessarily equate to improved patient outcomes and radical negative margins may not confer additive survival benefit over narrow negative margins 13. Furthermore, in cutaneous melanoma, lymph node dissections in the absence of macroscopic disease have not been shown to improve survival 14. Survival in mucosal melanomas is not usually determined by local disease but by metastatic disease, which occurs in the majority of patients regardless of local interventions. In that context, the role of the surgical oncologist is to achieve local control with the least extensive surgical insult, whilst maximising quality of life and early recovery. Due to their anatomical location, radical resections of melanomas are accompanied by a considerable risk of post-operative morbidity in terms of continence, sexual dysfunction and their resultant psychosocial impact. Hence, the key questions that must be answered in determining the optimal management of potentially curative disease are whether an initial radical approach improves survival in these patients and, if not, how loco-regional disease may be best controlled whilst maximising a patient’s quality of life.

Given the lack of consensus as to the optimal treatment for these patients, the UK-based charity Melanoma Focus initiated a guideline development programme for mucosal melanomas, including those affecting the anorectum. As part of that process, this systematic review and meta-analysis was performed to determine whether: (1) oncological outcomes differ between radical and conservative management of anorectal melanoma and (2) what is the impact of these strategies on the patient’s quality of life.

**Methods**

This systematic review was undertaken as part of development for UK guidelines on AUG melanoma developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE methodology). The protocol for the systematic review was developed by the Guideline Development Group comprising expertise in medical, clinical and surgical oncology; general, colorectal, plastic and reconstructive surgery; technical systematic review and meta-analysis; and patient experience. The protocol followed the PICO format, specifying Population, Intervention(s), Comparison(s), and Outcomes. The protocol specified that evidence from systematic reviews, randomised controlled trials and non-randomised observational studies comparing the effectiveness of radical surgery with local surgery for people with anorectal melanoma (stage 0-III) would be considered for inclusion in this review. Outcomes deemed as critical for patients undergoing surgical treatment were overall survival, disease-free survival, local recurrence, quality of life and patient-reported outcomes. Additional outcomes of interest were morbidity and negative resection rate. Where possible, direct pairwise meta-analyses were conducted using Cochrane Review Manager (RevMan5) software, with the outcomes presented in forest plots. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk, RR) for dichotomous outcomes. A random-effects analysis model was used when the presence of heterogeneity could not be explained by pre-specified sub-group analysis (margins, stage, anatomical location, and thickness). This study’s methodology has been accredited by The National Institute for Health and Clinical Excellence (NICE) and further details, including search terms and the databases used, can be found on the Melanoma Focus website (<https://melanomafocus.com/wp-content/uploads/2017/04/Melanoma-Focus-Methods-Manual-V4.2-FINAL.pdf>).

**Results**

Our literature search identified a total of 74 studies, of which 27 were suitable for inclusion in our analyses, including 1,301 patients with primary anorectal melanoma (Figure 1). The demographics of these studies are summarised in Table 1. No randomised controlled trials were identified. Due to the non-randomised nature of the evidence, the included studies offer more potential for bias - a major contributor to the quality rating for the body of evidence. The evidence as a whole is at very high risk of bias due to the non-randomised, observational nature of cohorts and the case-series designs. Many of the comparison surgery groups differed at baseline in their level of other potential confounders (e.g. stage of disease and tumour size) and patient groups were managed differently alongside their surgical procedure (e.g. adjuvant therapy). All these factors are likely to have confounded the relationship between the surgical procedure undertaken and the critical patient outcomes. There were also widely varying durations of follow-up times within the analyses as well as in the comparative populations. These factors are taken into account in the GRADE quality rating for the evidence associated with each outcome.

*Overall survival*

A total of 23 studies, including 895 patients, directly compared overall survival between patients undergoing WLE or APR 15-37. Meta-analysis of these studies demonstrated no significant difference in overall survival between either strategy (Risk ratio (RR) 0.80, 95% CI 0.60-1.07, p = 0.13) (Figure 2). No significant heterogeneity was noted between these studies (I2 9%, p = 0.35). Although there was some evidence to suggest favourable outcomes with WLE, the quality of the evidence was very low and it must be concluded that there is no evidence to support superior overall survival with either technique. Subgroup analyses did not demonstrate any differences in outcomes based on stage or achieving microscopically negative (R0) margins. Two of the studies identified performed their own multivariable analyses, with neither finding the initial surgical strategy to be independently prognostic of overall survival 18,32.

*Disease-free survival*

A total of 7 studies reported on disease-free survival, with very low quality evidence suggesting no significant difference found in outcomes between WLE and APR (RR 1.08, 95% CI 0.61-1.91, p = 0.79) (Figure 3) 16,17,30,33,35,38,39. No significant heterogeneity was noted between these studies (I2 0%, p = 0.73). Subgroup analyses did not demonstrate any differences in outcomes based on stage or achieving microscopically negative (R0) margins. The duration of disease-free survival was reported in all 7 studies, with the median duration ranging from 2.5 to 23.2 months following APR and 5 to 16 months following WLE.

*Local recurrence*

A total of 19 studies reported on local recurrence. Again, very low quality evidence suggested no significant difference in outcomes between either APR or WLE (RR 0.71, 95% CI 0.44-1.14, p = 0.16) (Figure 4) 15-18,20,23,24,27,29-31,35-41. Marked heterogeneity between these studies (I2 78%, p < 0.00001) contributed to the very low quality rating of the evidence. Although on subgroup analysis a stronger effect was noted in those patients with R0 margins, this was not significant (RR 0.49, 95% CI 0.23-1.04, p = 0.06) and was again compromised by marked heterogeneity between studies. In addition, no significant differences were found in a subgroup analysis based on stage at intervention.

*Quality of life*

None of the studies identified in this literature reported the outcomes of either surgical strategy on quality of life.

**Discussion**

There is debate with regard to the optimal primary surgical strategy in patients with anorectal melanoma, with consensus limited in part by the rarity of this condition and volume of quality evidence. Using the best available evidence, we have found no significant improvement in local disease control or survival with the use of radical primary surgery in the form of APR over survival post-local excision or WLE.

Although none of the studies identified compared morbidity or quality of life outcomes after APR or WLE, the morbidity associated with radical anorectal resections for rectal pathology is well documented 42-44. In the absence of any evidence of a benefit from radical primary surgery in anorectal melanoma, and the limited life expectancy in this patient group, the surgeon is duty bound to achieve negative resection margins in the least radical fashion possible. This is not to say APR has no role in the management of this disease, and may indeed be the most suitable option in those patients in whom WLE may result in an unacceptable compromise of anorectal function or in those with evidence of sphincter invasion or mesorectal lymphatic involvement. However, a default primary strategy of WLE with the option of either repeated WLE or APR as salvage in the event of local recurrence should be the primary operative strategy in the majority of patients.

The potential role of adjuvant immunotherapy and targeted therapies in the management of ARM is a further area of uncertainty. At this time, there is no robust evidence of a benefit of adjuvant therapy in ARM. Whilst the benefits of these agents have been demonstrated in clinical trials that did not exclude patients with mucosal melanomas, the number of such patients was small and, as such, caution should be used when extrapolating data from these trials into clinical practice 45,46. The evidence of reduced efficacy of immunotherapy in mucosal compared with cutaneous melanoma further supports such caution 47. Given the lack of evidence to demonstrate a benefit, or lack there of, of adjuvant systemic therapies in patients with ARM, the use of these agents should only take place in the context of a clinical trial. At this time, an alternative strategy following an initial conservative surgical resection would be close surveillance with regular proctoscopy, flexible sigmoidoscopy, MR pelvis and CT scanning, with consideration given to combination immunotherapy in the event of an inoperable local recurrence and/or distant relapse.

This systematic review is part of a comprehensive guideline for the diagnosis and management of anorectal and urogenital mucosal melanomas in partnership, developed in the UK with the charity Melanoma Focus (<https://melanomafocus.com/activities/mucosal-guidelines/mucosal-melanoma-resources/>). In addition to recommendations regarding surgical strategy, due to rarity and complexity of these tumours, it is also recommended that patients with anorectal melanomas discussed at a multidisciplinary tumour board meeting with attending anorectal surgical and melanoma expertise. This may not only help to standardise the management of these patients, but also, given the rapid evolution of the management of melanoma as a whole, facilitate the inclusion of patients with anorectal mucosal melanoma in future clinical trials.

If the management of patients with ARM is to improve, the identification and utilisation of real world data from these patients is vital. A key research recommendation from the guidelines referenced above is the establishment of a national registry of anorectal and urogenital melanomas within the UK, with a proposed minimum dataset. The UK currently lags behind other European countries in which such registries already exist and have allowed international collaborations to further optimise the use of real world data from patients with melanoma 50.

In conclusion, we found no benefit in radical surgery over WLE, if WLE is feasible and appropriate in the particular setting, in a systematic review and meta-analysis of the available literature using GRADE methodology. Evidence regarding quality of life in anorectal melanoma is absent and it is vital future prospective studies include such data. Given the rarity and complexity of anorectal melanoma, centralisation/specialisation may be beneficial, as would the consideration of recently published guidelines.

**Table 1. Demographics of the included studies.** \*median unless otherwise specified. OS = overall survival; DFS = disease-free survival; LR = local recurrence; ns = not specified.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Lead author** | **Country of origin** | **Total patients** | **Endpoints** | **Follow up (months)\*** |
| Antoniuk 1993 | USA | 15 | OS, DFS, LR | ns |
| Belli 2008 | Italy | 40 | OS, DFS, LR | 75 |
| Bullard 2003 | USA | 15 | OS, DFS, LR | 16 |
| Che 2011 | China | 56 | OS, LR | 14-144 (range) |
| Choi 2011 | Korea | 19 | OS | ns |
| David 2007 | India | 17 | LR | 8 |
| Hicks 2014 | USA | 18 | OS, LR | 18.5 |
| Iddings 2010 | USA | 183 | OS | ns |
| Ishizone 2008 | Japan | 79 | OS | ns |
| Knowles 2016 | Australia | 16 | DFS, LR | 18 yrs |
| Konstadoulakis 1995 | USA | 15 | OS, LR | ns |
| Luna-Perez 1996 | Mexico | 15 | OS, LR | ns |
| Malik 2004 | USA | 19 | OS | ns |
| Moozar 2003 | Canada | 14 | OS | 28 |
| Nilsson 2010 | Sweden | 251 | OS, LR | ns |
| Perez 2013 | USA | 65 | DFS, LR | 20 |
| Pessaux 2004 | France | 40 | OS | ns |
| Ramakrishnan 2008 | India | 63 | OS, LR | ns |
| Ross 1990 | USA | 32 | OS, DFS, LR | ns |
| Roumen 1996 | Netherlands | 63 | OS, LR | ns |
| Slingluff 1990 | USA | 24 | OS | 26.4 |
| Thibault 1997 | USA | 50 | DFS, LR | 66 months – 44 yrs (range) |
| Wang 2013 | China | 43 | OS, DFS | 20 |
| Weyandt 2003 | Germany | 16 | OS | 15-119 (range) |
| Yen 2013 | Taiwan | 22 | OS, DFS, LR | ns |
| Zhang 2010 | China | 54 | OS, LR | 25 |
| Zhou 2010 | China | 57 | OS, LR | 37 |

**Figure legends**

**Figure 1.** PRISMA flowchart demonstrating included and excluded studies. This systematic review was undertaken as part of developing comprehensive guidelines on the diagnosis and management of anorectal and urogenital mucosal melanomas. Given the rare nature of these conditions and that the evidence is almost exclusively limited to observational studies, it was decided to carry out a wide single search with the aim of capturing all the research evidence. Therefore, the flowchart represents records for mucosal melanoma broadly until the assessment of full-text papers where the anorectal melanoma papers can be specifically identified.

**Figure 2.** Comparison of overall survival following APR with WLE in anorectal melanoma.

**Figure 3.** Comparison of disease-free survival following APR with WLE in anorectal melanoma.

**Figure 4.** Comparison of local recurrence-free survival following APR with WLE in anorectal melanoma.

**References**

1. Moore R. Recurrent melanosis of the rectum, after previous removal from the verge of the anus, in a man aged sixty-five. *The Lancet.* 1857;69(1751):290.

2. Chen H, Cai Y, Liu Y, et al. Incidence, Surgical Treatment, and Prognosis of Anorectal Melanoma From 1973 to 2011: A Population-Based SEER Analysis. *Medicine (Baltimore).* 2016;95(7):e2770.

3. Cagir B, Whiteford MH, Topham A, Rakinic J, Fry RD. Changing epidemiology of anorectal melanoma. *Dis Colon Rectum.* 1999;42(9):1203-1208.

4. McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. *Cancer.* 2005;103(5):1000-1007.

5. Ragnarsson-Olding BK, Nilsson PJ, Olding LB, Nilsson BR. Primary ano-rectal malignant melanomas within a population-based national patient series in Sweden during 40 years. *Acta Oncol.* 2009;48(1):125-131.

6. Falch C, Stojadinovic A, Hann-von-Weyhern C, et al. Anorectal malignant melanoma: extensive 45-year review and proposal for a novel staging classification. *J Am Coll Surg.* 2013;217(2):324-335.

7. Weinstock MA. Epidemiology and prognosis of anorectal melanoma. *Gastroenterology.* 1993;104(1):174-178.

8. Bello DM, Smyth E, Perez D, et al. Anal versus rectal melanoma: does site of origin predict outcome? *Dis Colon Rectum.* 2013;56(2):150-157.

9. 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;117(20):4747-4755.

10. Zhang S, Gao F, Wan D. Effect of misdiagnosis on the prognosis of anorectal malignant melanoma. *J Cancer Res Clin Oncol.* 2010;136(9):1401-1405.

11. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin.* 2017;67(2):93-99.

12. Kuo JC. Immune checkpoint inhibitors in the treatment of advanced mucosal melanoma. *Melanoma Manag.* 2017;4(3):161-167.

13. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347(16):1227-1232.

14. Coit D. The Enigma of Regional Lymph Nodes in Melanoma. *N Engl J Med.* 2017;376(23):2280-2281.

15. Antoniuk PM, Tjandra JJ, Webb BW, Petras RE, Milsom JW, Fazio VW. Anorectal malignant melanoma has a poor prognosis. *Int J Colorectal Dis.* 1993;8(2):81-86.

16. Belli F, Gallino GF, Lo Vullo S, Mariani L, Poiasina E, Leo E. Melanoma of the anorectal region: the experience of the National Cancer Institute of Milano. *Eur J Surg Oncol.* 2009;35(7):757-762.

17. Bullard KM, Tuttle TM, Rothenberger DA, et al. Surgical therapy for anorectal melanoma. *J Am Coll Surg.* 2003;196(2):206-211.

18. Che X, Zhao DB, Wu YK, et al. Anorectal malignant melanomas: retrospective experience with surgical management. *World J Gastroenterol.* 2011;17(4):534-539.

19. Choi BM, Kim HR, Yun HR, et al. Treatment outcomes of anorectal melanoma. *J Korean Soc Coloproctol.* 2011;27(1):27-30.

20. Hicks CW, Pappou EP, Magruder JT, et al. Clinicopathologic Presentation and Natural History of Anorectal Melanoma: A Case Series of 18 Patients. *JAMA Surg.* 2014;149(6):608-611.

21. 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(1):40-44.

22. Ishizone S, Koide N, Karasawa F, et al. Surgical treatment for anorectal malignant melanoma: report of five cases and review of 79 Japanese cases. *Int J Colorectal Dis.* 2008;23(12):1257-1262.

23. Konstadoulakis MM, Ricaniadis N, Walsh D, Karakousis CP. Malignant melanoma of the anorectal region. *J Surg Oncol.* 1995;58(2):118-120.

24. Luna-Perez P, Rodriguez DF, Macouzet JG, Labastida S. Anorectal malignant melanoma. *Surg Oncol.* 1996;5(4):165-168.

25. Malik A, Hull TL, Floruta C. What is the best surgical treatment for anorectal melanoma? *Int J Colorectal Dis.* 2004;19(2):121-123.

26. Moozar KL, Wong CS, Couture J. Anorectal malignant melanoma: treatment with surgery or radiation therapy, or both. *Can J Surg.* 2003;46(5):345-349.

27. Nilsson PJ, Ragnarsson-Olding BK. Importance of clear resection margins in anorectal malignant melanoma. *Br J Surg.* 2010;97(1):98-103.

28. Pessaux P, Pocard M, Elias D, et al. Surgical management of primary anorectal melanoma. *Br J Surg.* 2004;91(9):1183-1187.

29. Ramakrishnan AS, Mahajan V, Kannan R. Optimizing local control in anorectal melanoma. *Indian J Cancer.* 2008;45(1):13-19.

30. 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(3):313-316.

31. Roumen RM. Anorectal melanoma in The Netherlands: a report of 63 patients. *Eur J Surg Oncol.* 1996;22(6):598-601.

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

33. Wang M, Zhang Z, Zhu J, et al. Tumour diameter is a predictor of mesorectal and mesenteric lymph node metastases in anorectal melanoma. *Colorectal Dis.* 2013;15(9):1086-1092.

34. Weyandt GH, Eggert AO, Houf M, Raulf F, Brocker EB, Becker JC. Anorectal melanoma: surgical management guidelines according to tumour thickness. *Br J Cancer.* 2003;89(11):2019-2022.

35. Yen CI, Chen HH, Chiang SF, et al. Anorectal melanoma: review of 22 consecutive cases. *Hepatogastroenterology.* 2013;60(121):89-93.

36. Zhang S, Gao F, Wan D. Abdominoperineal resection or local excision? a survival analysis of anorectal malignant melanoma with surgical management. *Melanoma Res.* 2010;20(4):338-341.

37. 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(5):585-588.

38. Perez DR, Trakarnsanga A, Shia J, et al. Locoregional lymphadenectomy in the surgical management of anorectal melanoma. *Ann Surg Oncol.* 2013;20(7):2339-2344.

39. Thibault C, Sagar P, Nivatvongs S, Ilstrup DM, Wolff BG. Anorectal melanoma--an incurable disease? *Dis Colon Rectum.* 1997;40(6):661-668.

40. David AW, Perakath B. Management of anorectal melanomas: a 10-year review. *Trop Gastroenterol.* 2007;28(2):76-78.

41. Knowles J, Lynch AC, Warrier SK, Henderson M, Heriot AG. A case series of anal melanoma including the results of treatment with imatinib in selected patients. *Colorectal Dis.* 2016;18(9):877-882.

42. Nissan A, Guillem JG, Paty PB, et al. Abdominoperineal resection for rectal cancer at a specialty center. *Dis Colon Rectum.* 2001;44(1):27-35; discussion 35-26.

43. Hendren SK, O'Connor BI, Liu M, et al. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. *Ann Surg.* 2005;242(2):212-223.

44. Juul T, Ahlberg M, Biondo S, et al. Low anterior resection syndrome and quality of life: an international multicenter study. *Dis Colon Rectum.* 2014;57(5):585-591.

45. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *N Engl J Med.* 2017;377(19):1813-1823.

46. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N Engl J Med.* 2017;377(19):1824-1835.

47. D'Angelo SP, Larkin J, Sosman JA, et al. Efficacy and Safety of Nivolumab Alone or in Combination With Ipilimumab in Patients With Mucosal Melanoma: A Pooled Analysis. *J Clin Oncol.* 2017;35(2):226-235.

48. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med.* 2019.

49. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med.* 2018;378(19):1789-1801.

50. Weichenthal M, van Akkooi ACJ, Mohr P, et al. EUMelaReg: A European platform for outcome research on real world treatment data of patients with advanced melanoma. *Ann Oncol.* 2018;29(8:459).