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## Examining the impact of body mass index on overall survival in vulvar, vaginal and other mucosal melanomas: a retrospective cohort study

Analiza wpływu wskaźnika masy ciała na przeżycie całkowite u pacjentek z czerniakiem sromu, pochwy i innych czerniaków błon śluzowych: retrospektywne badanie kohortowe

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### Abstract

**Aim of the study:** In this retrospective cohort study we have examined differences in survival profiles with respect to the body mass index in patients with mucosal melanoma on immune checkpoint inhibitor therapy. **Materials and methods:** The primary outcome included the association between the body mass index and overall survival in patients with metastatic mucosal melanoma. The secondary outcomes included the clinical presentation and management of vulvar and vaginal melanomas with oral and anorectal mucosal melanomas, as well as the surgical and radiological management of vulvar and vaginal melanomas. Kaplan–Meier analysis and log-rank test were used for the assessment of overall survival. **Results:** The results showed that patients with mucosal melanoma whose body mass index was  $\geq 25$  had better overall survival ( $p = 0.02$ ). Overall survival was different between vulvar/vaginal vs. oral mucosal melanoma ( $p = 0.02$ ). Overall survival was not different between vulvar/vaginal vs. anorectal melanoma ( $p = 0.77$ ). Some immune toxicities were specific to patients with vulvar/vaginal melanoma. **Conclusions:** Obesity is associated with improved survival in patients with metastatic mucosal melanoma, although findings can be heterogeneous depending on the subtype of mucosal melanoma.

**Keywords:** body mass index, vulvar melanoma, vaginal melanoma, immune checkpoint inhibitors

### Streszczenie

**Cel pracy:** W ramach retrospektywnego badania kohortowego oceniano różnice w profilu przeżycia w odniesieniu do wskaźnika masy ciała u pacjentek z czerniakiem błony śluzowej leczonych inhibitorami immunologicznego punktu kontrolnego. **Materiał i metody:** Jako pierwszorzędowy punkt końcowy analizowano zależność między wskaźnikiem masy ciała a przeżyciem całkowitym u pacjentek z przerzutowym czerniakiem błony śluzowej. Drugorzędowe punkty końcowe obejmowały obraz kliniczny i sposób leczenia czerniaków sromu i pochwy w porównaniu z czerniakami błony śluzowej jamy ustnej oraz odbytu i odbytnicy, a także leczenie chirurgiczne i radiologiczne czerniaków sromu i pochwy. Ocenę przeżycia całkowitego przeprowadzono przy wykorzystaniu analizy Kaplana–Meiera i testu *log-rank*. **Wyniki:** W badaniu stwierdzono lepsze przeżycie całkowite ( $p = 0,02$ ) u pacjentek z czerniakiem błony śluzowej, u których wskaźnik masy ciała wynosił  $\geq 25$ . Odnotowano różnice w przeżyciu całkowitym między czerniakiem sromu/pochwy a czerniakiem błony śluzowej jamy ustnej ( $p = 0,02$ ). Nie wykazano natomiast różnic w przeżyciu całkowitym między czerniakiem sromu/pochwy a czerniakiem odbytu i odbytnicy ( $p = 0,77$ ). Niektóre objawy toksyczności immunologicznej były swoiste dla pacjentek z czerniakiem sromu/pochwy. **Wnioski:** Otyłość wiąże się z lepszym przeżyciem u pacjentek z przerzutowym czerniakiem błony śluzowej, chociaż w zależności od podtypu nowotworu wyniki mogą być zróżnicowane.

**Słowa kluczowe:** wskaźnik masy ciała, czerniak sromu, czerniak pochwy, inhibitory immunologicznego punktu kontrolnego

## INTRODUCTION

Despite being a negative prognostic factor in a majority of cancers, body mass index (BMI) is associated with favorable outcome in metastatic melanoma treated with immune checkpoint inhibitors (ICIs)<sup>(1,2)</sup>. However, these favorable outcomes have largely been observed in patients with metastatic melanoma or cutaneous melanoma, and few studies to date have examined this association in patients with mucosal melanoma. Furthermore, ICIs such as anti-cytotoxic T-lymphocyte-4 (anti-CTLA-4) and anti-programmed cell death protein-1 (anti-PD-1) have been of recent interest for metastatic vulvar and vaginal melanoma. Multiple clinical trials are currently examining the role of ICIs for treating this rare, aggressive disease with poor long-term clinical outcomes<sup>(3)</sup>. In this retrospective cohort study, we have examined differences in survival profiles in patients with mucosal melanoma with respect to the BMI. We have further performed a subgroup analysis of the survival and toxicity profiles of vulvar and vaginal melanoma vs. oral and anorectal mucosal melanoma on ICI therapy.

## MATERIALS AND METHODS

This retrospective chart review involved patients with metastatic melanoma who were at least 18 years of age and received  $\geq 1$  dose of ICIs (either PD-1 and/or CTLA-4 inhibitors) at our institution from June 2012 to December 2018. Research Ethics Approval was obtained from the Sunnybrook Health Sciences Centre. The primary outcome included the association between the BMI and overall survival (OS) in patients with metastatic mucosal melanoma. The secondary outcomes included the comparison of clinical presentation and management of vulvar and vaginal melanomas with oral and anorectal mucosal melanomas, as well as surgical and radiological management of vulvar and vaginal melanomas. Kaplan–Meier analysis and log-rank test were used for OS.

## RESULTS

A total of 235 patients with metastatic melanoma were examined, including 11/235 (4.7%) with vulvar and vaginal mucosal melanoma, 7/235 (3.0%) with oral mucosal melanoma, 4/235 (1.7%) with anorectal mucosal melanoma, and the remainder melanomas of cutaneous, desmoplastic, and unknown subtypes. The mutation status, prior therapies, toxicities, treatment outcomes for vulvar and vaginal melanoma vs. oral mucosal melanoma and anorectal mucosal melanoma are compared in Tab. 1. The total number of reported immune-related adverse events (irAEs) was 9 in patients with vulvar and vaginal melanoma, 4 in patients with oral mucosal melanoma, and 1 in anorectal mucosal melanoma. Importantly, some irAEs such as hypothyroidism, renal and urinary disorders, as well as musculoskeletal and

connective tissue disorders were reported in patients with vulvar and vaginal melanoma, but not in patients with oral or anorectal mucosal melanoma.

Amongst the patients with mucosal melanoma, overweight and obese patients with the BMI greater than or equal to 25 had a significantly higher OS (52.5 years) compared to patients whose BMI was  $< 25$  (47.6 years;  $p = 0.02$ , chi-square statistics = 5.05, degrees of freedom = 1). Furthermore, the subgroup analysis resulted in a statistically significant difference in OS between vulvar and vaginal melanoma vs. oral mucosal melanoma ( $p = 0.02$ , chi-square statistic = 5.63, degrees of freedom = 1), though without a significant difference in OS between vulvar and vaginal vs. anorectal melanoma ( $p = 0.77$ , chi-square statistic = 0.08, degrees of freedom = 1).

	Vulvar and vaginal melanoma; frequency (%)	Oral mucosal melanoma; frequency (%)	Anorectal mucosal melanoma; frequency (%)
<b>Mutation status</b>			
<i>NRAS</i>	1/11 (9.1)	0	1/4 (25.0)
<i>c-KIT</i>	1/11 (9.1)	1/7 (14.3)	0
<i>BRAF</i>	1/11 (9.1)	1/7 (14.3)	0
Total	3/11 (27.3)	2/7 (28.6)	1/4 (25.0)
<b>Prior therapy</b>			
Surgery	9/11 (81.8)	4/7 (57.1)	3/4 (75.0)
Radiation therapy	7/11 (63.6)	3/7 (42.9)	1/4 (25.0)
<b>irAEs</b>			
Gastrointestinal	2/9 (22.2)	1/4 (25)	0
Cutaneous	1/9 (11.1)	1/4 (25)	0
Pneumonitis	1/9 (11.1)	1/4 (25)	0
Hypothyroidism	1/9 (11.1)	0	0
Nervous system disorder	1/9 (11.1)	0	0
Renal and urinary disorder	1/9 (11.1)	1/4 (25)	0
Musculoskeletal and connective tissue disorder	1/9 (11.1)	0	0
Pneumonitis	0	0	1/1 (100)
Unknown	1/9 (11.1)	0	0
Total reported	9/9 (100)	4/4 (100)	1/1 (100)
<b>Treatment outcome</b>			
Response to treatment	1/11 (9.1)	0	0
Progressive disease	6/11 (54.5)	4/7 (57.1)	2 (50.0)
Death	0	1/7 (14.3)	1 (25.0)
Unknown	4/11 (36.4)	2/7 (28.6)	1/4 (25.0)
Total	11/11 (100)	7/7 (100)	4/4 (100)
<i>BRAF</i> – human gene that encodes the protein B-raf; <i>c-KIT</i> – human gene that encodes the receptor kinase protein known as tyrosine-protein kinase KIT; <i>irAEs</i> – immune-related adverse events; <i>NRAS</i> – human gene that encodes the protein N-Ras.			

Tab. 1. Comparison of mutation status, prior therapy, irAEs, and treatment outcomes for vulvar and vaginal, oral and anorectal mucosal melanoma

## DISCUSSION

Our results illustrate a favorable relationship between increased BMI values and OS in patients with mucosal melanoma on ICI therapy. The mechanism underlying the association between the BMI and survival is not well-understood, though some sources note that obesity may promote leptin-mediated T-cell dysfunction, which is reversed by the blockade of the PD-1<sup>(4)</sup>. Furthermore, a recent review on melanoma patients illustrates that the factors that induce an immunosuppressive microenvironment could in turn make these patients more susceptible to ICI therapy<sup>(1)</sup>. A retrospective study of 423 patients with metastatic melanoma showed a significant survival benefit in overweight and obese patients receiving combination immunotherapy but heterogeneous trends for other treatment types<sup>(5)</sup>. As our results focus more specifically on patients with mucosal melanoma, our findings shed light on potential contributors to such heterogeneous trends, such as the melanoma subtype. In addition, a body composition analysis on melanoma patients identifies inferior clinical outcomes in patients with sarcopenic obesity ( $p = 0.04$ ), as well as high total adipose tissue index ( $p = 0.02$ ), a difference that was particularly strong in women compared to men<sup>(2)</sup>. These findings merit further investigation of the association between body composition and survival in patients with mucosal melanoma on ICI therapy.

A greater percentage of patients with vulvar and vaginal melanoma received surgical or radiation therapy prior to ICI therapy, compared to patients with oral mucosal melanoma. Of note, radiation is more commonly used in the management of anorectal melanoma as well as vulvar and vaginal melanoma compared with oral mucosal melanoma, which is related to difficulties obtaining clear surgical margins for the former subtypes<sup>(6)</sup>. Recent studies indicate better outcomes in patients treated with surgery or a combination of surgery and radiotherapy, compared to radiation monotherapy<sup>(7)</sup>. The complex nature of vulvovaginitectomies, as well as the associated complications and morbidity, could explain the rare prevalence of these procedures despite favorable treatment outcomes<sup>(7)</sup>.

Other studies support the presence of a *KIT* mutation which encodes a transmembrane receptor tyrosine kinase in both mucosal melanomas as well as other cancers such as gastrointestinal stromal tumors<sup>(8)</sup>. Similarly, the *BRAF* gene encodes the B-raf protein and has a much lower incidence in mucosal melanoma compared to cutaneous melanoma<sup>(8)</sup>. Despite the low incidence of targetable *KIT* and *BRAF* mutations, it is essential that mutational analysis is carried out in all cases of metastatic vulvar and vaginal melanoma in order to identify further options for systemic therapy. Furthermore, these findings support the use of targeted therapies such as imatinib for *KIT* mutations in mucosal melanomas<sup>(9)</sup>.

While literature sources demonstrate a more aggressive behavior and poorer prognosis in mucosal melanoma

compared to cutaneous melanoma<sup>(10)</sup>, our results indicate that there is wide heterogeneity within some subtypes of mucosal melanoma, as demonstrated by the significant difference in OS between vulvar/vaginal melanoma and oral melanoma, but not anorectal melanoma.

## CONCLUSIONS

With the increasing use of ICIs in the management of mucosal melanomas, and vulvar and vaginal melanomas in particular, a greater understanding of the clinical outcomes is imperative for the gynecologists who may treat these patients in routine clinical practice.

### Conflict of interest

Rossanna C. Pezo reports the receipt of honoraria from Pfizer, EMD Serono and Novartis, and research funding from Merck, and serves on advisory boards for Astra Zeneca, Exact Sciences, Lilly, Myriad Genetics, Pfizer and Novartis, all outside the submitted work. The other authors report no conflicts of interest.

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