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Treatment outcomes of vulvar and vaginal melanoma at an NCCN institution between 1993 and 2021

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ABSTRACT

Background: Vulvar melanoma and vaginal melanoma are rare and difficult to treat. We describe the last three decades in a cohort predominantly treated surgically with adjuvant therapy.
Methods: All new patients between 1993 and 2021 followed until 2024. Collection of demographic and oncologic data allowed comparisons and Kaplan-Meier method was used to evaluate overall survival (OS) and progression free survival (PFS) stratified by adjuvant therapy type, diagnosis before and after 2011, and between vulvar and vaginal melanomas.
Results: Consultation for 63/72 patients (87.5 %) were for primary treatment. Most patients had vulvar melanoma (50/72, 69.4 %), received surgery (65/72, 90.3 %), and adjuvant treatment (40/72, 55.6 %) with immunotherapy, chemotherapy, and/or targeted therapy. Median survival for 63 patients presenting for primary treatment was 54.2 months, and 9/13 patients who were disease free after five years later received adjuvant immunotherapy. Survival did not vary by adjuvant therapy type or diagnosis after 2011 but was significantly less for vaginal melanoma. Following recurrence seven patients experienced complete response including three patients receiving combined nivolumab with ipilimumab and two nivolumab alone experienced.
Conclusions: Survival was not significantly different by adjuvant therapy type or after 2011. Most patients who were disease-free five years after surgery had received adjuvant therapy. Seven patients experienced complete responses to therapy after recurrence of whom five received immune checkpoint inhibitors. Although survival is not improved as in cutaneous melanomas by immune checkpoint inhibitors, signal continues for the use of immune checkpoint inhibitors in gynecologic melanomas.

1. Introduction

Gynecologic melanomas differ significantly from squamous cell carcinomas of the vulva and vagina with management principles extrapolated from experience with cutaneous melanoma (Abu-Rustum et al., 2024; Wohlmuth and Wohlmuth-Wieser, 2021). Moreover, vulvar melanoma and vaginal melanoma have been characterized as having distinct biologies which in part predict lower response rates to treatment than cutaneous melanoma (Boer et al., 2021; Hou et al., 2017; Wohlmuth et al., 2020). Genomic differences include a relatively lower mutational burden which predicts lesser responsiveness to immune checkpoint inhibitor (ICI) therapy (Sun et al., 2023).

Surgery is utilized for resectable, locoregional disease, and stage is the most important prognostic factor (Phillips et al., 1994). Neoadjuvant chemotherapy (specifically carboplatin and paclitaxel) has been used to improve rates of complete resection (Abu-Rustum et al., 2024). Over the past decades, adjuvant treatment of melanoma has included observation, cytotoxic chemotherapy, targeted therapy, immunotherapies like interferon, and immune checkpoint inhibitors (ICIs) alone or in combination (Boer et al., 2021; Wohlmuth et al., 2020). Beginning in 2011,

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Table 1
Demographic and clinical presentation at first consultation at mayo clinic.

Characteristic	
1a: Overall	N = 72
Age at first relevant consultation at Mayo Clinic (years), mean (SD)	63.9 (11.9)
Race	
White	66 (91.7)
Other	2 (2.8)
Unknown	4 (5.5)
Ethnicity	
Not Hispanic/Latina	55 (76.4)
Hispanic/Latina	0
Unknown	17 (23.6)
Type of primary cancer	
Vaginal	22 (30.6)
Vulvar	50 (69.4)
Type of cancer at first Mayo consult	
Primary	63 (87.5)
Recurrent	9 (12.5)
1b: Among those with primary disease at first consultation at Mayo Clinic	N = 63
AJCC stage (8th edition)	
I	1 (1.6)
II	25 (39.7)
IIIA	3 (4.8)
IIIB	6 (9.5)
IIIC	9 (14.3)
IV	4 (6.3)
Unknown or not documented	15 (23.8)
Neoadjuvant therapy	
No	54 (85.7)
Yes	9 (14.3)
Surgery	
No	7 (11.1)
Yes	56 (88.9)
Age at surgery (years), mean (SD)	64.6 (12.0)
Adjuvant therapy	
No	28 (44.4)
Yes	35 (55.6)
Adjuvant cytotoxic chemotherapy*	7/35 (20.0)
Adjuvant immunotherapy	27/35 (77.1)
Adjuvant targeted therapy*	1/35 (2.9)
Adjuvant therapy type unknown	1/35 (2.9)
1c: Among those with recurrent disease at first consultation at Mayo Clinic	N = 9
Previous neoadjuvant chemotherapy	0
Previous neoadjuvant immunotherapy	0
Previous surgery	9 (100.0)
Previous adjuvant cytotoxic chemotherapy†	2 (22.2)
Previous adjuvant immunotherapy†	4 (44.4)
Previous adjuvant targeted therapy	0
Previous second line treatment	
No	5 (55.6)
Yes	3 (33.3)
Unknown	1 (11.1)
Type of previous second line treatment	
Cytotoxic chemotherapy	0
Immunotherapy	3/3 (100.0)
Targeted therapy	0
Subsequent line of treatment AFTER the first Mayo consult	
Second line (with an indication of recurrent disease)	7 (77.8)
Third line (with an indication of progressive disease)	2 (22.2)
Type of subsequent line treatment AFTER first Mayo consult	
Cytotoxic chemotherapy	2 (22.2)
Immunotherapy	6 (66.7)
Targeted therapy	0
Surgery only	1 (11.1)

In section 1a, demographic data is presented for all patients treated for primary (next analyzed in 1b) or recurrent disease (1c) at their first consultation at Mayo Clinic. Section 1b includes a patient who received both chemotherapy and targeted therapy as concurrent adjuvant treatment.
Abbreviations: AJCC, The American Joint Committee on Cancer; SD, standard deviation. Results presented as N (%) unless otherwise specified.
* 1 patient received both chemotherapy and targeted therapy.
† 1 patient received both chemotherapy and immunotherapy.

ICIs demonstrated overall survival improvements in cutaneous melanoma (D'Angelo et al., 2017; Hamid et al., 2018; Robert et al., 2015b; Wolchok et al., 2017a). While ICIs were implemented for all melanomas, other targeted therapies also emerged (Robert et al., 2015a). A recent review of 198 women with vulvar melanoma in the Netherlands and United Kingdom between 1990 and 2017 reviewed early experience with ICIs including one patient treated in the adjuvant setting and 28 who received ICIs or targeted therapies after first recurrence (Boer et al., 2021). Clinical response to treatment with anti-PD1 therapies (2/11, 18 %) and CTLA-4 therapies (1/5, 20 %) led to the conclusion that further study and clinical trials are needed (Boer et al., 2021).

Due to the rarity of vulvar and vaginal melanomas, prospective trials will need to prioritize which treatments to study based upon periodic retrospective analyses. Herein, we describe our institutions experience in treating gynecologic melanomas, stratify survival as before and after 2011 (ICIs debut and period of increasing treatment heterogeneity), and compare survival by anatomic sites of origin. A final description of clinical response to targeted therapy and ICIs in the adjuvant and recurrent settings was also performed to provide guidance towards a class of agents demonstrating greater clinical activity.

2. Methods

Following institutional IRB approval, all patients seen at the Mayo Clinic in Rochester, Minnesota, between January 1993 (beginning of electronic medical record) and October 2021 for vulvar and vaginal melanomas were identified and followed until July 2024. Patients with primary melanoma of a different anatomic site or those lacking record of their previous treatments prior to consultation were excluded. Patients with previous treatment at other centers transferring care were also included but analyzed separately to avoid biasing survival to that of a recurrent cohort.

Demographic and clinicopathologic data were abstracted. Cohorts were analyzed based upon disease status at first consultation at Mayo Clinic (primary versus recurrent), adjuvant treatment type, and subsequent management at the time of first recurrence or progression. Stage followed the definitions provided from the American Joint Committee on Cancer (AJCC) 8th edition. For patients who received additional lines of therapy, we describe response to treatment as determined by the treating oncologist using the revised response evaluation criteria in solid tumors (RECIST) guidelines (Schwartz et al., 2016).

Data were summarized using standard descriptive statistics [mean and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables]. Overall survival (OS) and progression-free survival (PFS) were evaluated for patients initiating treatment at our institution and included stratification by tumor origin, adjuvant treatment type, and treatment before 2011 or after (2011+). Description of survival time-to-event summaries utilized the median and interquartile range (IQR). Survival analyses were performed using the Kaplan-Meier method with survival curves compared across subgroups with the log-rank test. Time-to-event was calculated from the date of first consultation to the date of death or last follow-up for OS and from the date of diagnosis to the date of recurrence or last follow-up for PFS and p-values < 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics and therapies

In the study interval, 72 patients met inclusion criteria (Table 1A) with 63 initiating treatment at their first consultation (primary patients; Table 1B) versus 9 who presented for management of recurrent disease (recurrent patients; Table 1C). The majority had vulvar (n = 50, 69.4 %, including 7 recurrent patients) versus vaginal melanoma (n = 22, 30.6 %, including 2 recurrent patients). Across all patients, the mean age at first consultation was 63.9 years (range 32–99) and the majority were

Table 2
Adjuvant therapy details among patients presenting with primary disease at first consultation at Mayo Clinic.

Characteristic	N = 63
No adjuvant therapy	28
Received adjuvant therapy	35
Adjuvant chemotherapy[†]	7
Carboplatin and Paclitaxel/Nab-paclitaxel	3
Cisplatin and Temozolomide	3
Cisplatin	1
Adjuvant immunotherapy	27
Ipilimumab and Nivolumab	9
Nivolumab	5
Pembrolizumab	3
Other[*]	10
Adjuvant targeted therapy (Bevacizumab) [†]	1
Unknown type of adjuvant therapy received	1

Adjuvant treatment selection for patients treated for primary disease at Mayo Clinic is displayed including 10 patients who received:
*Other combinations: GM-CSF (n = 7), interferon (n = 2), and clinical trial: double-controlled study looking at vaccine/placebo and GM-CSF/placebo (n = 1).
[*] Other included granulocyte macrophage colony-stimulating factor (GM-CSF) (n = 7), Interferon (n = 2), and clinical trial: double-controlled study looking at vaccine/placebo and GM-CSF/placebo (n = 1).
[†] 1 patient received both chemotherapy and targeted therapy.

white (n = 66, 91.7 %).

For the 63 primary patients, most received surgical management (n = 56, 88.9 %). Nine primary patients started neoadjuvant chemotherapy with two undergoing planned surgery. There was one stage I (1.6 %), 25 stage II (39.7 %), 18 stage III (28.6 %), and 4 stage IV (6.3 %) patients; stage was unavailable or not documented in 15 (23.8 %). Most primary patients received adjuvant therapy (n = 35, 55.6 %) consisting of immunotherapy (n = 27, 77.1 %), cytotoxic chemotherapy only (n = 6, 17.1 %), combined chemotherapy with targeted therapy (n = 1, 2.9 %), and treatment type was unknown for one patient. See Table 2 for all adjuvant treatment selections.

3.2. Overall survival within the primary patient cohort

Death within five years of diagnosis was documented in 35 patients at a median of 22.5 months (IQR 12.7–40.7 months). The median duration of follow-up for the remaining 28 patients was 73.0 months (IQR 56.0–101.3 months). Overall survival across the entire cohort was 88.9 % (95 % CI, 81.5–97.0 %) at 1 year, 63.1 % (95 % CI, 52.1–76.3 %) at 3 years, and 41.3 % (95 % CI, 30.3–56.3 %) at 5 years (Fig. 1A). Median survival was 54.2 months, and 13 patients were disease free five years after adjuvant therapy in which nine patients received adjuvant immunotherapy (Supplemental Table 1).

Diagnosis before 2011 occurred in 22/63 patients versus in 2011+ for 41/63. Overall survival for diagnosis before 2011 did not differ from 2011+ (log-rank p = 0.56, Fig. 1B). Overall survival at 1, 3, and 5 years for before 2011 and 2011+ were, respectively: 95.5 % (95 % CI, 87.1–100.0 %), 59.1 % (95 % CI, 41.7–83.7 %), and 35.8 % (95 % CI, 20.3–63.1 %) versus 85.4 % (95 % CI, 75.2–96.9 %), 65.3 % (95 % CI, 52.1–81.8 %), and 44.0 % (95 % CI, 30.4–63.8 %). When comparing by site of cancer origin (vulvar versus vaginal), OS was significantly worse for patients with vaginal melanoma (log-rank p < 0.01; Supplemental Fig. 1).

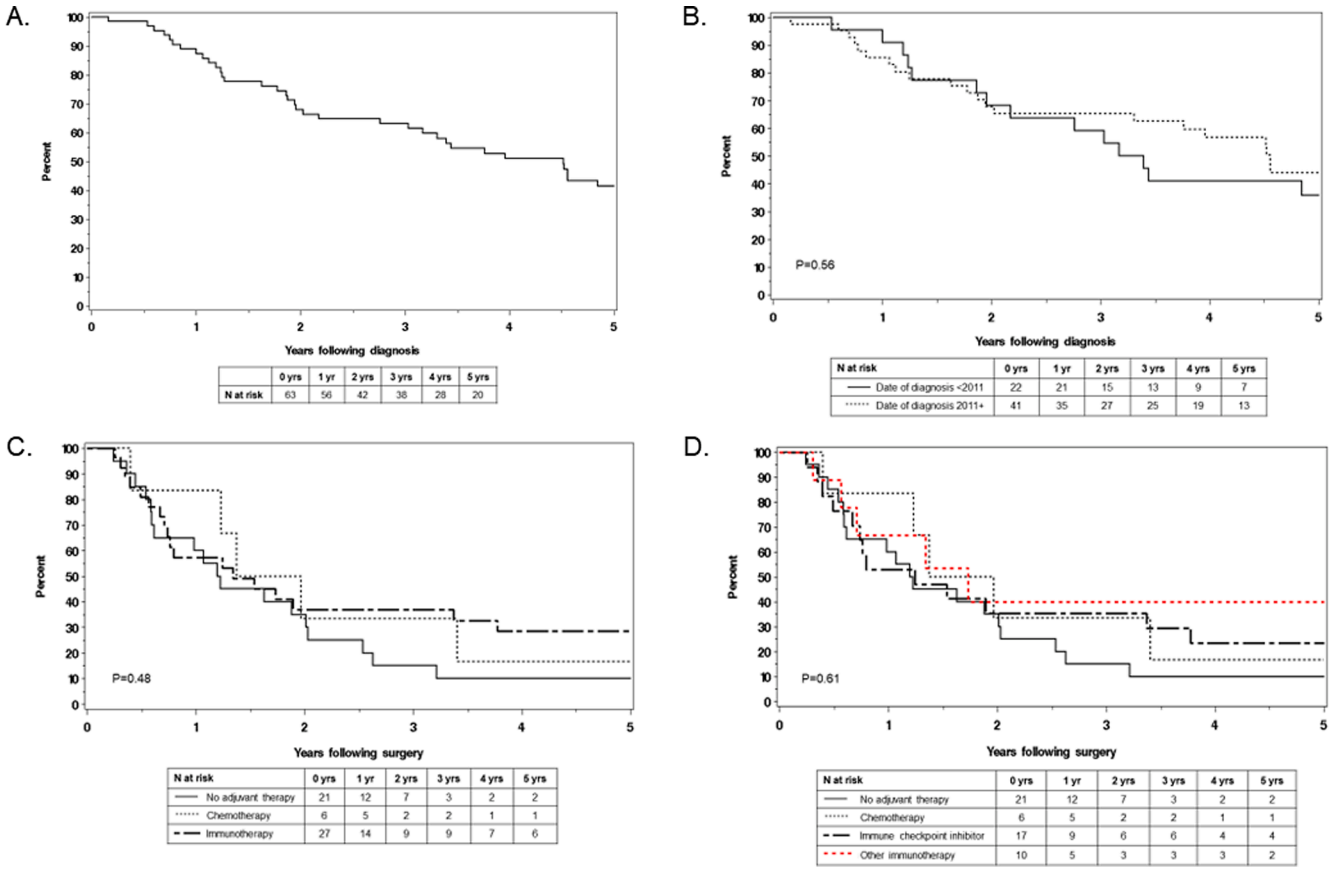

Fig. 1. OS among patients with primary disease at first consultation at Mayo Clinic across the study period is shown in panel 1A. OS is compared prior to and after 2011 in panel 1B. PFS by adjuvant therapy following surgery are analyzed in 1C in which all immunotherapies are reviewed together, and panel 1D in which ICIs are separated from other forms of immunotherapy. There is no significant difference between groups in panels 1B, 1C, nor 1D.

Table 3
Therapy for Progression or Recurrence.

Therapy	Total N = 60	Primary N = 51	Recurrent N = 9
Surgery only (N = 9)	9	8	1
Type of subsequent line targeted therapy (N = 9)			
Bevacizumab	1	1	–
Other*	8	8	–
Type of subsequent line chemotherapy (N = 13)			
Carboplatin and Paclitaxel/Nab-paclitaxel	5	5	–
Temozolomide	8	6	2
Type of subsequent line immunotherapy (N = 32)			
Ipilimumab	2	2	–
Ipilimumab and Nivolumab	10	8	2
Ipilimumab, Nivolumab, and Other (Talimogene laherparepvec)	1	–	1
Nivolumab	6	5	1
Pembrolizumab	5	5	–
Other†	8	6	2
Unknown subsequent therapy type received (N = 1)	1	1	–

NOTE: Some patients have more than one type of subsequent line therapy which is why counts add up to more than the unique patient count (primary: 1 patient received both chemotherapy and immunotherapy, 1 patient received chemotherapy and targeted therapy, 2 received immunotherapy and targeted therapy). Includes all patients treated for recurrent/progressive disease, regardless of whether they presented with primary or recurrent/progressive disease. Four patients received two types of treatment simultaneously (2 with immunotherapy and targeted therapy, 1 with chemotherapy and immunotherapy, 1 with immunotherapy and targeted therapy) are counted in multiple categories and therefore table adds up to 64 and not 60.

* Other targeted therapy: Cobimetinib (n = 1), Dabrafenib/Trametinib (n = 2), Imatinib (n = 3), Indoximod (n = 1) and Nilotinib (n = 1).

† Other immunotherapy: Atezolizumab (n = 1), GM-CSF (n = 3), IL-2 (n = 1), TSR-042 (anti-PD-1) + TSR-022 (anti-TIM-3) (n = 1), CDX1140 (CD40 antibody) (n = 1), and Interferon (n = 1).

3.3. Progression-free survival of the primary patient cohort

The analysis of PFS included the 54 primary patients who had surgery and excluded one with persistent disease and one with inadequate documentation of follow-up. Recurrence or progression within five years following diagnosis occurred in 41 patients (75.9 %). The median duration of follow-up for the remaining 13 patients without recurrence or progression within five years was 65.0 months (IQR 55.8–80.9 months).

Adjuvant therapy was characterized as follows: observation (n = 21, 38.9 %), chemotherapy (n = 6, 11.1 %), and immunotherapy (n = 27, 50.0 %). Targeted therapy was received by one patient in combination with chemotherapy and was included in the adjuvant chemotherapy subgroup. Median PFS was 14.5 months for observation, 20.1 months for cytotoxic chemotherapy, and 16.1 months for adjuvant immunotherapy (all types). No significant difference in the survival curves was found when comparing the adjuvant therapy subgroups (log-rank p = 0.48; Fig. 1C). To compare immunotherapies before and after 2011, Fig. 1D evaluated PFS by separating immunotherapies into ICIs (ipilimumab, nivolumab, and/or pembrolizumab) and other immunotherapy (GM-CSF, interferon, or a clinical trial vaccine with/without GM-CSF). When comparing survival curves among patients utilizing adjuvant ICIs (n = 17, median PFS 14.9 months), other immunotherapy (n = 10, median PFS 20.8 months), observation, and chemotherapy subgroups, we did not find a significant difference in PFS (log-rank p = 0.61).

3.4. Clinical response by treatment for recurrent or progressive disease

Subsequent therapies in patients who experienced recurrence or progression are summarized in Table 3 (60 patients total from the combined primary and recurrent cohorts; 9 with surgery only and 51 with subsequent therapy). Survival was then calculated using the 50 patients with known treatment type. Disease progression or recurrence occurred in 37 with a median time from treatment initiation of 2.9 months (IQR: 1.9–5.0 months). Of the remaining 9 patients who did not progress or recur, the median time from treatment to last relevant follow-up was 5.8 months (IQR, 2.6–24.0 months).

Some patients received multiple types of therapy and were then included in more than one category. The most utilized subsequent systemic therapy after recurrence or progression was immunotherapy (n = 32), followed by chemotherapy (n = 13) and targeted therapy (n = 9). Most immunotherapy regimens selected after recurrence or disease progression were ICIs (25 regimens including ipilimumab, nivolumab, pembrolizumab, or atezolizumab alone or in combination), with the most common regimen being ipilimumab with nivolumab (n = 10/51, 19.6 %). Temozolomide was the most common chemotherapy regimen (n = 8/51, 15.7 %) followed by carboplatin with paclitaxel or nab-paclitaxel (n = 5/51, 9.8 %). Targeted therapies, utilized by nine patients, included seven different agents alone or in combination.

The most common clinical response to subsequent lines of therapy included progression on therapy (Table 4). There were seven complete responses to treatment by RECIST criteria including one of six patients (16.7 %) on targeted therapy only, five of 31 patients (16.1 %) on immunotherapy ± targeted therapy, and one of 12 patients (8.3 %) receiving chemotherapy ± targeted therapy. When described by drug or drug combination, complete response occurred in six primary patients with vulvar melanoma: three patients receiving combination nivolumab and ipilimumab, two patients receiving nivolumab alone, and one patient on dabrafenib and trametinib with a positive *BRAF* mutation. One recurrent patient treated for vulvar melanoma had a complete response with temozolomide. Somatic tumor testing was available for three of the seven patients experiencing a complete response, and there were targetable mutations identified aside from the single *BRAF* mutation.

4. Discussion

Although we did not identify a survival difference between therapy

Table 4
Best Radiographic Response to Treatment After First Progression or Recurrence*.

Response to treatment per clinician, N (%)	Targeted therapy only N = 6	Chemotherapy ± targeted therapy N = 12	Immunotherapy ± targeted therapy N = 31	Immunotherapy and chemotherapy N = 1
Complete	1 (16.7)	1 (8.3)	5 (16.1)	0
Partial	0	0	0	0
Stable disease	1 (16.7)	1 (8.3)	0	0
Progressive disease	3 (50.0)	8 (66.7)	20 (64.5)	1 (100.0)
Other	0	0	2 (6.5)	0
Not documented	1 (16.7)	2 (16.7)	4 (12.9)	0

Based upon 60 patients from Table 3 not including those receiving surgery (nine) or unknown therapy type (one).
Summary of response to therapy based upon treatment type and presentation status at first consultation at Mayo Clinic. Excludes nine patients who never received systemic therapy and one patient with fo0072 whom the choice of therapy was unknown.

subgroups or improvements after 2011, nine of 13 patients reaching five-year disease-free status received adjuvant immunotherapy. Moreover, five complete responses in primary patients treated for recurrent disease included three that received ipilimumab with nivolumab and two nivolumab alone. Additionally, one recurrent patient experienced a complete response with temozolomide. One primary patient had a *BRAF* mutation and experienced a complete response with dabrafenib and trametinib after somatic tumor testing. There was not a significant difference in survival between adjuvant chemotherapy, immunotherapy, or observation in a cohort predominantly consisting of stage II disease or greater.

The median survival in our primary patients was available for vaginal melanoma only as patients with vulvar melanoma had a continued survival above 50 % at the time of analysis. Median overall survival for vaginal melanoma in our cohort was 22.5 months and consistent with Joste et al. who reported a median survival difference favoring vulvar melanoma (62.4 versus 22.8 months) and hazard ratio for death of vaginal versus vulvar site of 8.56 (95 % CI, 1.95–37.64, $p < 0.05$). Our cohort is also consistent with a Surveillance, Epidemiology, and End Results Program (SEER) database review of 1863 patients with melanoma of all types, which demonstrated a survival advantage using ICIs in cutaneous melanoma but not in gynecologic melanomas (Wohlmuth et al., 2020). There was no survival advantage by class of agent in our patients which differs from a recent retrospective cohort of 198 patients describing a survival advantage using ICIs in patients with unresectable disease (Boer et al., 2021; Schwartz et al., 2016), and this difference is most likely related to nearly all primary patients having been treated first by complete resection rather than initial medical therapy or palliation.

Strengths of our study include the timeframe spanning 1993–2021 with follow-up through 2024. Almost two-thirds of the primary patients were diagnosed after 2011 and received therapies with current priority in melanoma. Across three decades, patients received treatment consistent with strategies for advanced melanomas as represented by the decrease in GM-CSF use after 2010 and utilization of ipilimumab and nivolumab combination which was recently shown to extend OS in advanced melanoma over ipilimumab alone (Wolchok et al., 2017b). Demographic factors for our patients are comparable to other reports with a diagnosis typically in white patients during the seventh decade of life. Both before and after 2011, most patients had resected disease improving our ability to evaluate ICIs in a comparable adjuvant setting across the study interval. Finally, heterogeneity in practice was reduced by treatment predominantly at a single center.

Limitations of the present study include its retrospective and descriptive nature which lacks statistical power for formal comparisons between treatments and groups. Constraints of Kaplan-Meier survival modeling included small cohort sizes and treatment received at multiple institutions. We attempted to work within these constraints to limit bias by focusing survival analyses on primary patients. Owing to the rarity of gynecologic melanomas, their study together may limit our ability to detect differences between them. The number of complete responses to therapy were encouraging, however could be misleading as if taken alone as the overall rates of response by agent ranged from 8.3 % to 16.7 %. Somatic tumor testing was only performed in three of seven patients with a complete response and only identified a single *BRAF* mutation.

While survival differences by treatment type were not observed, 10 of 13 patients disease free five years after surgery had received adjuvant treatment. Additionally, following recurrence or progression, complete response occurred in 16.1 % of patients treated with immune checkpoint inhibitors which was comparable to other agents. Although *BRAF* mutations are infrequent for gynecologic melanomas, somatic tumor testing identified a targetable *BRAF* mutation leading to complete response with dabrafenib and trametinib. After recurrence or progression, complete response to treatment was most frequently observed using nivolumab in combination with ipilimumab.

CRediT authorship contribution statement

Stuart A. Ostby: Writing – original draft, Methodology, Formal analysis, Data curation. **Saige Daniel:** Writing – review & editing, Data curation. **Eleftheria Kalogera:** Writing – review & editing, Supervision. **Luigi De Vitis:** Writing – review & editing. **Angela J. Fought:** Writing – review & editing, Visualization, Formal analysis. **Michaela E. McGree:** Writing – review & editing, Visualization, Software, Formal analysis, Data curation. **Carrie L. Langstraat:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Matthew S. Block:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2024.101483.

References

Abu-Rustum, N.R., Yashar, C.M., Arend, R., Barber, E., Bradley, K., Brooks, R., Campos, S.M., Chino, J., Chon, H.S., Crispens, M.A., Damast, S., Fisher, C.M., Frederick, P., Gaffney, D.K., Gaillard, S., Giuntoli, R., Glaser, S., Holmes, J., Howitt, B.E., Kendra, K., Lea, J., Lee, N., Mantia-Smaldone, G., Mariani, A., Mutch, D., Nagel, C., Nekhlyudov, L., Podoll, M., Rodabaugh, K., Salani, R., Schorge, J., Siedel, J., Sisodia, R., Soliman, P., Ueda, S., Urban, R., Wethington, S.L., Wyse, E., Zanotti, K., McMillian, N., Espinosa, S., 2024. Vulvar cancer, version 3.2024, NCCN clinical practice guidelines in oncology. J. Natl. Compr. Canc. Netw. 22, 117–135. https://doi.org/10.6004/JNCCN.2024.0013.

Boer, F.L., ten Eikelder, M.L.G., van Geloven, N., Kapiteijn, E.H., Gaarenstroom, K.N., Hughes, G., Nooij, L.S., Jozwiak, M., Tjiong, M.Y., de Hullu, J.M.A., Galaal, K., van Poelgeest, M.I.E., 2021. Evaluation of treatment, prognostic factors, and survival in 198 vulvar melanoma patients: implications for clinical practice. Gynecol. Oncol. 161, 202–210. https://doi.org/10.1016/J.YGYNO.2021.01.018.

D'Angelo, S.P., Larkin, J., Sosman, J.A., Lebbé, C., Brady, B., Neyns, B., Schmidt, H., Hassel, J.C., Hodi, F.S., Lorigan, P., Savage, K.J., Miller, W.H., Mohr, P., Marquez-Rodas, I., Charles, J., Kaatz, M., Sznol, M., Weber, J.S., Shoushtari, A.N., Ruisi, M., Jiang, J., Wolchok, J.D., 2017. Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J. Clin. Oncol. 35, 226–235. https://doi.org/10.1200/JCO.2016.67.9258.

Hamid, O., Robert, C., Ribas, A., Hodi, F.S., Walpole, E., Daud, A., Arance, A.S., Brown, E., Hoeller, C., Mortier, L., Schachter, J., Long, J., Ebbinghaus, S., Ibrahim, N., Butler, M., 2018. Antitumour activity of pembrolizumab in advanced mucosal melanoma: a post-hoc analysis of KEYNOTE-001, 002, 006. Br. J. Cancer 119, 670–674. https://doi.org/10.1038/S41416-018-0207-6.

Hou, J.Y., Baptiste, C., Hombalegowda, R.B., Tergas, A.I., Feldman, R., Jones, N.L., Chatterjee-Paer, S., Bus-Kwolfski, A., Wright, J.D., Burke, W.M., 2017. Vulvar and vaginal melanoma: a unique subclass of mucosal melanoma based on a comprehensive molecular analysis of 51 cases compared with 2253 cases of nongynecologic melanoma. Cancer 123, 1333–1344. https://doi.org/10.1002/CNCR.30473.

Phillips, G.L., Bundy, B.N., Okagaki, T., Kucera, P.R., Stehman, F.B., 1994. Malignant melanoma of the vulva treated by radical hemivulvectomy. A prospective study of the gynecologic oncology group. Cancer 73, 2626–2632. https://doi.org/10.1002/1097-0142(19940515)73:10<2626::aid-cncr2820731026>3.0.co;2-u.

Robert, C., Karaszewska, B., Schachter, J., Rutkowski, P., Mackiewicz, A., Stroiakovski, D., Lichinitser, M., Dummer, R., Grange, F., Mortier, L., Chiarion-Sileni, V., Drucis, K., Krajsova, I., Hauschild, A., Lorigan, P., Wolter, P., Long, G.V., Flaherty, K., Nathan, P., Ribas, A., Martin, A.-M., Sun, P., Crist, W., Legos, J., Rubin, S.D., Little, S.M., Schadendorf, D., 2015a. Improved overall survival in melanoma with combined dabrafenib and trametinib. N. Engl. J. Med. 372, 30–39. https://doi.org/10.1056/NEJMOA1412690.

Robert, C., Schachter, J., Long, G.V., Arance, A., Grob, J.J., Mortier, L., Daud, A., Carlino, M.S., McNeil, C., Lotem, M., Larkin, J., Lorigan, P., Neyns, B., Blank, C.U., Hamid, O., Mateus, C., Shapira-Frommer, R., Kosh, M., Zhou, H., Ibrahim, N., Ebbinghaus, S., Ribas, A., 2015b. Pembrolizumab versus ipilimumab in advanced melanoma. N. Engl. J. Med. 372, 2521–2532. https://doi.org/10.1056/NEJMOA1503093.

Schwartz, L.H., Litière, S., De Vries, E., Ford, R., Gwyther, S., Mandrekar, S., Shankar, L., Bogaerts, J., Chen, A., Dancey, J., Hayes, W., Hodi, F.S., Hoekstra, O.S., Huang, E.P., Lin, N., Liu, Y., Therasse, P., Wolchok, J.D., Seymour, L., 2016. RECIST 1.1 – update

and clarification: from the RECIST committee. Eur. J. Cancer 62, 132. https://doi.org/10.1016/J.EJCA.2016.03.081.

Sun, W., Liu, K., Zhou, H., Zhao, F., Dong, Y., Xu, Y., Kong, Y., Wang, M., Cheng, X., Chen, Y., 2023. Whole-exome sequencing reveals mutational profiles of anorectal and gynecological melanoma. Med. Oncol. 40 https://doi.org/10.1007/S12032-023-02192-6.

Wohlmuth, C., Wohlmuth-Wieser, I., 2021. Vulvar melanoma: molecular characteristics, diagnosis, surgical management, and medical treatment. Am. J. Clin. Dermatol. 22, 639–651. https://doi.org/10.1007/S40257-021-00614-7.

Wohlmuth, C., Wohlmuth-Wieser, I., May, T., Vicus, D., Gien, L.T., Laframboise, S., 2020. Malignant melanoma of the vulva and vagina: a US population-based study of 1863 patients. Am. J. Clin. Dermatol. 21, 285. https://doi.org/10.1007/S40257-019-00487-X.

Wolchok, J.D., Chiarion-Sileni, V., Gonzalez, R., Rutkowski, P., Grob, J.-J., Cowey, C.L., Lao, C.D., Wagstaff, J., Schadendorf, D., Ferrucci, P.F., Smylie, M., Dummer, R., Hill, A., Hogg, D., Haanen, J., Carlino, M.S., Bechter, O., Maio, M., Marquez-Rodas, I., Guidoboni, M., McArthur, G., Lebbé, C., Ascierto, P.A., Long, G.V., Cebon, J., Sosman, J., Postow, M.A., Callahan, M.K., Walker, D., Rollin, L., Bhore, R., Hodi, F.S., Larkin, J., 2017a. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N. Engl. J. Med. 377, 1345–1356. https://doi.org/10.1056/NEJMOA1709684.

Wolchok, J.D., Chiarion-Sileni, V., Gonzalez, R., Rutkowski, P., Grob, J.-J., Cowey, C.L., Lao, C.D., Wagstaff, J., Schadendorf, D., Ferrucci, P.F., Smylie, M., Dummer, R., Hill, A., Hogg, D., Haanen, J., Carlino, M.S., Bechter, O., Maio, M., Marquez-Rodas, I., Guidoboni, M., McArthur, G., Lebbé, C., Ascierto, P.A., Long, G.V., Cebon, J., Sosman, J., Postow, M.A., Callahan, M.K., Walker, D., Rollin, L., Bhore, R., Hodi, F.S., Larkin, J., 2017b. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. New Engl. J. Med. 377, 1345–1356. https://doi.org/10.1056/NEJMOA1709684/SUPPL_FILE/NEJMOA1709684_DISCLOSURES.PDF.