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Original Article

Vulvar melanoma: an analysis of prognostic factors and treatment patterns

Ashley Albert,[1] **Anna Lee**,[2] **Robert Allbright**,[1] **Srinivasan Vijayakumar**[1]

[1]Department of Radiation Oncology, University of Mississippi Medical Center, Jackson, MS, USA
[2]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

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Correspondence to
Ashley Albert
Department of Radiation Oncology, University of Mississippi Medical Center, 350 W. Woodrow Wilson Drive, Suite 1600, Jackson, MS 39213, USA.
E-mail: Ashley.grv@gmail.com

ORCID iDs
Ashley Albert
https://orcid.org/0000-0002-7598-4142
Anna Lee
https://orcid.org/0000-0002-9114-1815
Robert Allbright
https://orcid.org/0000-0003-3049-717X
Srinivasan Vijayakumar
https://orcid.org/0000-0002-1678-9451

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ABSTRACT

Objective: Melanoma comprises 5% to 10% of vulvar cancers and prognosis is poor. The purpose of this study was to identify prognostic factors and treatment patterns for vulvar melanoma using the National Cancer Database (NCDB).
Methods: The NCDB was queried for patients with invasive vulvar melanoma from 2004–2015. Descriptive statistics were generated to describe clinical and treatment details. Multivariable Cox regression and the Kaplan-Meier method were used to examine overall survival (OS).
Results: 1,917 patients with vulvar melanoma met inclusion criteria. Median follow-up time was 32 months (range, 0–151 months). Older age, larger tumor size, advanced disease stage, increased Charlson-Deyo comorbidity score, and care at a non-academic center were independent predictors for decreased OS. Surgical management of the primary site, lymph node surgery, and insurance provided a significant survival benefit. Use of immunotherapy for vulvar melanoma has increased over time. Two-year OS with immunotherapy in patients with distant metastatic disease was higher, although this did not reach statistical significance (33% vs. 12%, p=0.054).
Conclusions: Vulvar melanoma has a poor prognosis for those with regional and distant metastatic disease. Extent of disease, tumor size, and patient age are important prognostic factors. Other favorable factors included insurance and surgical management. The use of immunotherapy has increased over time and may improve survival in those with distant disease. These data support further investigation into the role of immunotherapy for vulvar melanoma to optimize outcomes.

Keywords: Vulva; Melanoma; Immunotherapy; Prognostic Factors

INTRODUCTION

The most common histology of vulvar cancer is squamous cell carcinoma followed by melanoma which is estimated to comprise approximately 5%–10% of vulvar cancers and portends a worse prognosis as compared to squamous cell carcinoma [1,2]. Given the rarity of this disease, treatment decisions are often extrapolated from cutaneous melanomas of other sites [1]. However data from the Surveillance Epidemiology and End Results (SEER) database indicates that vulvar

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melanomas may have distinct clinicopathologic features and survival patterns from cutaneous melanomas [3]. As such, additional efforts are needed to optimize outcomes for this rare entity.

Mucosal melanomas make up 1.4% of all melanomas and in contrast to cutaneous melanoma, risk factors for melanomas have not yet been identified [4,5]. They most commonly found in the vulva, the vagina, the anorectum, and the oral and nasal cavity [6]. Additionally, mucosal melanomas portend a worse prognosis as compared to cutaneous melanomas. The benefit of immunotherapy for cutaneous melanoma has been explored with much interest recently [7]. However, less data are available regarding the use of immunotherapy in mucosal melanomas including vulvar melanoma [8]. As such, we sought to identify treatment patterns and outcomes in a large cohort of patients with vulvar melanoma receiving care at Commission on Cancer (CoC) accredited facilities.

MATERIALS AND METHODS

The NCDB is a nationwide, hospital-based registry that consists of patients who received care at cancer centers accredited by the American College of Surgeons CoC and currently captures approximately 70% of all patients newly diagnosed with cancer [9,10]. The CoC's NCDB and the accredited facilities participating in the NCDB are the source of the de-identified data used in this study. However, they have not verified and are not responsible for the statistical validity or conclusions derived by the authors of this study. This project did not meet the definition of human subjects research and therefore intuitional review board approval was not required.

The NCDB allows for the identification of the tumor primary site based on the International Classification of Diseases for Oncology, Third Edition topography code. This was used to select patients with vulvar cancer. The NCDB was queried for patients with vulvar melanoma from 2004–2015 and demographic, clinical, and treatment details were obtained. Patient demographic details included age and race. Clinical and treatment details included tumor stage, tumor size, Charlson-Deyo comorbidity (CDCC) score, median income quartiles, percentage of adults in patient's zip code with no high school degree, county population, the categorization of academic or non-academic cancer center, U.S. region, insurance type, year of diagnosis, and the receipt of surgery, radiation, chemotherapy, and immunotherapy.

Vital status was available but not cause of death. Univariable and multivariable Cox regression was used to determine covariables associated with differences in overall survival (OS). Factors associated with a p-value <0.10 on univariable analysis were included in the multivariable analysis. The variables included in these analyses were age, stage (localized, regional, distant), tumor size, modified CDCC score (0, 1, 2, ≥3), race (white, black, other), facility type (academic, non-academic), U.S. regions (Northeast, Midwest, South, West), insurance status (none, private insurance, Medicare, Medicaid, other government, unknown), median income quartiles, percentage of adults in patient's zip code with no high school degree, county population, receipt of surgery of the primary site, receipt of surgery of the lymph nodes, receipt of radiation, chemotherapy, and immunotherapy.

A subgroup analysis for patients with vulvar melanoma based on extent of disease was performed. Variables included receipt of radiation, chemotherapy, and immunotherapy. OS curves comparing patients based on extent of disease were generated using the Kaplan-Meier

method and compared via the log-rank test. All analysis was performed using SPSS version 20 (IBM Inc., Armonk, NY, USA).

RESULTS

One thousand nine hundred seventeen patients with melanoma of the vulva met inclusion criteria. Patients with coding of stage 0/in-situ disease were excluded. Patients with unknown staging information were also excluded. Median follow-up time was 32 months (range, 0–152 months).

The median age of patients was 68 years (range, 18–90 years). Approximately three-quarters of patients had localized disease only. A large proportion (32%) of vulvar melanomas did not have tumor size recorded. The most common type of insurance was Medicare (54%) followed by private insurance (38%). The large majority of patients (95%) were treated with surgery whereas as smaller proportions received radiation, chemotherapy, or immunotherapy. Most patients (96%) had a CDCC score of 1 or less. A summary of additional demographic and clinical characteristics is found in **Table 1**.

Table 1. Select demographic and clinical characteristics (n=1,917)

Characteristics	Values
Median age (yr)	68
Stage	
Localized	1,359 (70.9)
Regional	419 (21.9)
Distant	139 (7.3)
Tumor size (cm)	
<2	605 (31.6)
2–3.9	402 (21.0)
≥4	298 (15.5)
Size unknown	612 (31.9)
Race	
White	1,800 (93.9)
Black	62 (3.2)
Other	55 (2.9)
CDCC score	
0	1,524 (79.5)
1	307 (16.0)
2	69 (3.6)
≥3	17 (0.9)
Insurance	
Not insured	45 (2.3)
Private Insurance	730 (38.1)
Medicaid	64 (3.3)
Medicare	1,028 (53.6)
Other government	10 (0.5)
Unknown	40 (2.1)
Median income quartiles	
<$38,000	262 (13.8)
$38,000–$47,999	456 (24.0)
$48,000–$62,999	552 (29.1)
$63,000+	629 (33.1)
% of adults in patient zip code with no high school degree	
≥21.0	251 (13.2)
13.0–20.9	467 (24.6)
7.0–12.9	674 (35.5)
<7.0	508 (26.7)

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Table 1. (Continued) Select demographic and clinical characteristics (n=1,917)

Characteristics	Values
Year of diagnosis	
2004–2007	467 (24.4)
2008–2011	652 (34.0)
2012–2015	798 (41.6)
Region	
Northeast	375 (19.6)
Midwest	487 (25.4)
South	628 (32.8)
West	427 (22.3)
Facility type	
Academic	854 (44.5)
Non-academic	1,063 (55.5)
County population	
Metro	1,508 (81.6)
Urban	304 (16.5)
Rural	36 (1.9)
Surgery	
No	95 (5.0)
Yes	1,822 (95.0)
Radiation	
No	1,718 (89.6)
Yes	199 (10.4)
Chemotherapy	
No	1,815 (94.7)
Yes	102 (5.3)
Immunotherapy	
No	1,727 (90.1)
Yes	190 (9.9)

Values are presented as number (%).
CDCC, Charlson/Deyo comorbidity.

The majority of patients with local and regional disease had surgery. Radiation was most often employed in the setting of regional disease. This was also the case for immunotherapy. Chemotherapy was most often used in the setting of distant disease. A summary of specific treatment details found in **Table 2**.

On multivariable Cox regression for patients with vulvar melanoma, older age (hazard ratio [HR]=1.03; 95% confidence interval [CI]=1.02–1.04; p<0.001), larger tumor size (HR=1.75; 95% CI=1.43–2.13; p<0.001), advanced disease stage, (HR=5.40; 95% CI=4.18–6.97; p<0.001), increased CDCC score (HR=2.65; 95% CI=1.53–4.58; p<0.001), and care at a non-

Table 2. Treatment details for vulvar melanoma

Variables	Localized (n=1,359)	Regional (n=419)	Distant (n=139)	p-value
Surgery				**<0.001**
No	29 (2.1)	15 (3.6)	51 (36.7)	
Yes	1,330 (97.9)	404 (96.4)	88 (63.3)	
Radiation				**<0.001**
No	1,285 (94.6)	339 (80.9)	94 (67.6)	
Yes	74 (5.4)	80 (19.1)	45 (32.4)	
Chemotherapy				
No	1,327 (97.6)	386 (92.1)	102 (73.4)	**<0.001**
Yes	32 (2.4)	33 (7.9)	37 (26.6)	
Immunotherapy				**<0.001**
No	1,289 (94.8)	316 (75.4)	122 (87.8)	
Yes	70 (5.2)	103 (24.6)	17 (12.2)	

Values are presented as number of patients (%). The p-values less than or equal to 0.05 are shown in bold.

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academic center (HR=1.23; 95% CI=1.07–1.42; p<0.004) were independent predictors for decreased OS. Radiation was associated with a survival decrement (HR=1.25; 95% CI=1.01–1.54; p=0.04). Surgical management of the primary site (HR=0.48; 95% CI=0.36–0.65; p<0.001), lymph node surgery (HR=0.83; 95% CI=0.72–0.97; p=0.020), private insurance (HR=0.61; 95% CI=0.39–0.96; p=0.03), and Medicare (HR=0.62; 95% CI=0.39–0.99; p=0.05) provided a significant survival benefit. Race, median income quartiles, education, and county population were not significantly associated with survival for vulvar melanoma. A summary of these data is found in **Table 3**.

Table 3. Univariable and multivariable Cox regression

Characteristics	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (1.03–1.04)	**<0.001**	1.03 (1.02–1.04)	**<0.001**
Stage				
Localized	1		1	
Regional	2.51 (2.16–2.94)	**<0.001**	2.48 (2.09–2.93)	**<0.001**
Distant	8.80 (7.09–10.9)	**<0.001**	5.40 (4.18–6.97)	**<0.001**
Tumor size (cm)				
<2	1			
2–3.9	1.77 (1.48–2.24)	**<0.001**	1.49 (1.23–1.80)	**<0.001**
≥4	2.49 (2.05–3.02)	**<0.001**	1.75 (1.43–2.13)	**<0.001**
Size unknown	1.07 (0.89–1.28)	0.498	1.03 (0.86–1.24)	0.768
Race				
White	1		1	
Black	1.40 (0.99–1.98)	0.054	1.27 (0.89–1.81)	0.196
Other	1.02 (0.67–1.56)	0.921	1.01 (0.66–1.56)	0.952
CDCC score				
0	1			
1	1.39 (1.17–1.66)	**<0.001**	1.21 (1.01–1.44)	**0.037**
2	2.47 (1.84–3.32)	**<0.001**	1.62 (1.20–2.19)	**0.002**
≥3	4.02 (2.36–6.83)	**<0.001**	2.65 (1.53–4.58)	**<0.001**
Insurance				
Not insured	1		1	
Private insurance	0.53 (0.34–0.82)	**0.004**	0.61 (0.39–0.96)	**0.033**
Medicaid	0.94 (0.54–1.63)	0.833	0.90 (0.51–1.58)	0.705
Medicare	1.14 (0.74–1.74)	0.555	0.62 (0.39–0.99)	**0.045**
Other government	0.60 (0.18–2.01)	0.408	0.62 (0.18–2.10)	0.441
Unknown	0.91 (0.49–1.70)	0.760	0.79 (0.41–1.52)	0.483
Median income quartiles				
<$38,000	1		1	
$38,000–$47,999	0.83 (0.67–1.02)	0.074	0.97 (0.78–1.21)	0.802
$48,000–$62,999	0.72 (0.58–0.88)	**0.002**	0.87 (0.70–1.09)	0.220
$63,000+	0.71 (0.58–0.87)	**0.001**	0.86 (0.70–1.07)	0.187
% of adults in patient zip code with no high school degree				
≥21.0	1		-	-
13.0–20.9	1.01 (0.91–1.26)	0.928	-	-
7.0–12.9	0.85 (0.69–1.05)	0.141	-	-
<7.0	0.86 (0.68–1.07)	0.171	-	-
Region				
Northeast	1		1	
Midwest	1.19 (0.97–1.45)	0.098	1.26 (1.02–1.56)	**0.033**
South	1.17 (0.97–1.43)	0.109	1.19 (0.96–1.46)	0.115
West	0.87 (0.70–1.08)	0.201	1.23 (0.98–1.56)	0.079
Facility type				
Academic	1		1	
Non-academic	1.21 (1.06–1.39)	**0.005**	1.23 (1.07–1.42)	**0.004**

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Table 3. (Continued) Univariable and multivariable Cox regression

Characteristics	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
County population				
Metro	1		-	-
Urban	1.11 (0.93–1.33)	0.242	-	-
Rural	1.08 (0.68–1.73)	0.743	-	-
Primary site surgery				
No	1		1	
Yes	0.21 (0.16–0.27)	**<0.001**	0.48 (0.36–0.65)	**<0.001**
Lymph node surgery				
No	1		1	
Yes	0.76 (0.66–0.87)	**<0.001**	0.83 (0.72–0.97)	**0.020**
Unknown	0.84 (0.27–2.60)	0.756	1.15 (0.36–3.63)	0.082
Radiation				
No	1		1	
Yes	2.14 (1.78–2.58)	**<0.001**	1.25 (1.01–1.54)	**0.036**
Chemotherapy				
No	1		1	
Yes	1.62 (1.23–2.13)	**<0.001**	0.81 (0.60–1.09)	0.166
Immunotherapy				
No	1		-	-
Yes	1.11 (0.89–1.38)	0.364	-	-

The p-values less than or equal to 0.05 are shown in bold.
CDCC, Charlson/Deyo comorbidity; CI, confidence interval; HR, hazard ratio.

Regarding the treatment of vulvar melanoma, 2-year OS survival with immunotherapy in patients with distant metastatic disease was higher as compared to those that did not receive immunotherapy although this did not reach statistical significance (33% vs. 12%, p=0.054). On univariable analysis, receipt of other treatments did not result in improved survival in any group as summarized in **Table 4**. Receipt of radiation was associated with decreased survival in patients with localized disease. Kaplan-Meier curves depicting survival in patients with vulvar melanoma based on localized, regional, and distant disease is shown in **Fig. 1**. Five-year OS for localized, regional, and distant disease was 55.8%, 22.2%, and 5.1%. The use of immunotherapy for vulvar melanoma has increased over time: 21.1% of patients received immunotherapy from 2004–2007, 27.4% of patients received immunotherapy from 2008–2011, and 51.6% of patients received immunotherapy from 2012–2015 (p=0.013).

DISCUSSION

In this large hospital-based database, we identified 1,917 cases of vulvar melanoma from the period of 2004–2015. Five-year OS for localized, regional, and distant disease was 55.8%, 22.2%, and 5.1%, respectively. There was a trend towards improved survival in patients with distant disease who received immunotherapy as compared to patients who did not, although not statistically significant.

Table 4. Univariable Cox regression for treatment type

Treatment type	Localized		Regional		Distant	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Radiation	1.96 (1.43–2.67)	**<0.001**	1.03 (0.74–1.41)	0.878	1.17 (0.79–1.75)	0.436
Chemotherapy	1.13 (0.62–2.05)	0.690	0.62 (0.38–1.01)	0.055	0.66 (0.42–1.03)	0.067
Immunotherapy	0.87 (0.60–1.28)	0.486	0.83 (0.61–1.13)	0.232	0.48 (0.22–1.03)	0.060

The p-values less than or equal to 0.05 are shown in bold.
CI, confidence interval; HR, hazard ratio.

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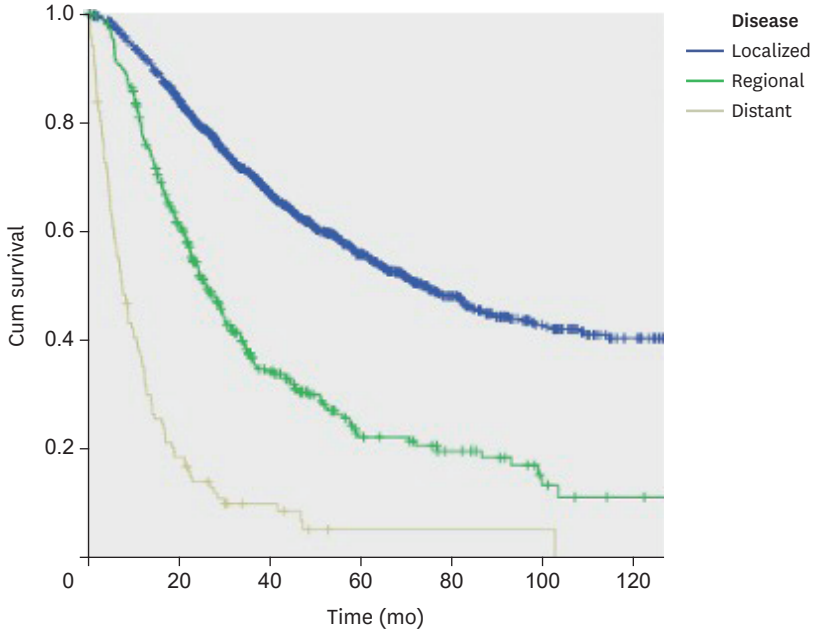

Fig. 1. Five year overall survival for patients based on disease extent. Localized=55.8%, regional=22.2%, distant=5.1%.

Approximately 94% of patients in the current series were white which is comparable to other studies investigating vulvar melanoma [3]. The median age in this series of patients was 68 which is somewhat higher than previous reports [1,11,12]. Increased age was found in the current series to be associated with decreased survival in vulvar melanoma which is consistent with other data [13]. As expected, increased CDCC score predicted for worse survival.

Increased tumor size was found to be a significant predictor of survival on Cox regression. Approximately one-third of patients with vulvar melanoma did not have the size of their tumor recorded in this hospital-based registry. Vulva and vaginal melanoma often present at a larger size as compared to other cutaneous melanomas and which may result in more challenging surgery and more difficulty when attempting to achieve negative surgical margins [14]. As such, size is a prognostic factor that should be taken into consideration when managing patients with vulvar melanoma. Neoadjuvant treatment with chemoradiation or radiation could potentially make resection more feasible for larger tumors however this strategy has not been investigated in depth for vulvar melanoma as it has been for squamous cell carcinoma of the vulva [15,16].

When stratified by disease stage, chemotherapy, immunotherapy, and radiation did not provide a survival benefit in any subgroup of patients. Radiation was associated with a survival decrement in localized disease likely due to selection bias involving patients with adverse features receiving adjuvant radiation. In a series of 98 patients with vulvar and vaginal cancer, no survival difference was found based on the receipt of adjuvant therapy [17]. Radiation has been to shown an improvement in local control for mucosal melanomas in some sites [5]. In the current analysis, there was a survival benefit for those patients that underwent surgery of the primary site consistent with other reports that define surgery as the mainstay of treatment for vulvar melanoma [4,17]. Previous reports have shown that surgical radicality is associated with increased morbidity with no increase in survival [12].

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Central tumor location and capillary lymphatic space involvement have been shown to predict for nodal positivity in patients with vulvar melanoma [11]. Additionally, pathologically positive groin nodes has been shown to be associated with a higher risk for disease recurrence and survival [11,13]. Likewise, we found that positive lymph nodes were associated with a survival decrement.

The Gynecologic Oncology Group prospective clinicopathologic study of vulvar melanoma could not make any recommendations regarding regional node resection [11]. Current data indicate that there is no role for lymph node dissection however the role of sentinel node biopsy is being investigated [18]. The NCDB defines regional lymph node surgery as removal, biopsy, or aspiration of regional lymph nodes at the time of surgery of the primary site or during a separate surgical event. In the current analysis, we found that receipt of lymph node surgery as previously defined reduced the risk of death among patients with vulvar melanoma as compared to no evaluation. We are unable to distinguish between sentinel lymph node biopsy and lymphadenectomy but these data indicate that lymph node evaluation of some type should be performed for vulvar melanoma.

In patients with advanced vulvar cancer, older age and insurance type have been shown to associated with decreased survival [19]. In a study using SEER data, race and ethnicity were not found to be associated with survival for patients with squamous cell carcinoma of the vulva [20]. However, Mert et al. [3] found a significant survival difference when comparing vulvar melanomas among black and nonblack patients, 33 months versus 58 months, respectively. In the current study, race was not found to be significantly associated with OS. Private insurance and Medicare were associated with improved survival and may reflect better access to care.

Additionally, we found that treatment at a non-academic center was associated with a survival decrement for patients with vulvar melanoma. As in the case for other rare tumors, clinical expertise found among specialists at academic institutions may be important for the management of vulvar melanoma. Additionally, treatment of patients at academic centers may be important so that patients can be enrolled on clinical trials when appropriate.

In the current analysis, we found a trend towards improved survival with the use of immunotherapy in patients with metastatic vulvar melanoma. A phase II trial with stage II–III mucosal melanoma included 21 patients with vulvar melanoma and randomized patients to receive no further treatment, high-dose interferon (HDI)-α, or temozolomide plus cisplatin following surgery [8]. This investigation found that HDI-α and temozolomide-based chemotherapy are effective and safe however temozolomide-based chemotherapy was more effective than HDI with respect to recurrence-free survival (RFS). In a series of 50 patients with vulvar and vaginal melanoma, adjuvant therapy including immunotherapy was not associated with improved OS or RFS [4].

In a pooled analysis of patients with mucosal melanoma and cutaneous melanoma receiving nivolumab and nivolumab with ipilimumab. nivolumab with ipilimumab showed greater efficacy than either agent alone however the activity was lower in mucosal melanoma as compared to cutaneous melanoma [21]. This analysis included 121 patients with mucosal melanoma. This is the largest analysis investigating the role of anti-programmed death-1 (PD-1) therapy in mucosal melanoma. The location of mucosal melanoma was not collected and the authors suggest the possibility of differences in response on anatomic location. The higher percentage of female patients in the mucosal melanoma group in that analysis may have been due to the number of vulvovaginal melanomas.

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A multi-institutional retrospective cohort analysis including patients with advanced (stage III and IV) acral and mucosal melanoma found that response rates to PD-1 blockade in patients with acral and mucosal melanomas were comparable to published rates of response in cutaneous melanoma [22]. This study included a total of 35 mucosal melanomas, 14 of which vulvovaginal. A small retrospective study of patients with metastatic melanoma of the lower genital tract from Italy showed that the response rate to immunotherapy was 28.5% [23].

A small series of patient with mucosal melanoma of the lower genital tract treated at Memorial Sloan Kettering Cancer Center demonstrated a favorable response to combined ipilimumab and radiation therapy suggesting that select patients could receive concurrent neoadjuvant radiation and checkpoint inhibition to decrease morbidity of surgical resection [15]. The synergism between immunotherapy used concurrently with radiation suggest that this may be a viable treatment strategy for vulvovaginal melanoma but additional data are needed.

Based on molecular analyses, the development of vulvar and vaginal melanoma may involve distinct molecular pathways [24]. As such, additional investigations may be needed in specific subsites of mucosal melanoma including vulvar melanoma to optimize treatment strategies. Additionally, given the higher rates of distant metastatic disease among patients with vulvar melanoma, further advances in the use of immunotherapy may prove beneficial for this group of patients who typically have a poor prognosis. Furthermore, patients with vulvar melanoma should continue to be enrolled on clinical trials involving immunotherapy agents in order to ascertain the most beneficial treatment for this rare tumor.

There are challenges and limitations with hospital-based registries. While data reporting to the NCDB is highly standardized, there may still be variances with data coding and abstraction. Detailed staging information was not present for all patients with vulva melanoma thus we opted to categorize patients into localized, regional, and distant disease groups. We were unable to determine the number, type, and does of immunotherapy agents that were used. Patient selection may have influenced those who were administered immunotherapy. We were unable to determine specific surgical details regarding extent of resection. Additionally, we were unable to distinguish between sentinel lymph node biopsy and lymph node dissection. We did not account for Breslow thickness and Clark level which may impact tumor recurrence [12]. Finally, data regarding salvage treatment and cause of death is not available in the NCDB.

Despite the aforementioned limitations, the use of a hospital-based databased allowed for the identification of a relatively large cohort of patients with a rare disease. As such, this study provides insight into prognostic factors and treatment strategies for this rare gynecologic tumor.

In conclusion, vulvar melanoma has a poor prognosis especially for those with regional and distant metastatic disease. Prognostic factors include disease stage, tumor size, patient age, comorbidities, and insurance status. Socioeconomic factors including median income quartiles, education, and county population were not significantly associated with survival for vulvar melanoma. Care at a non-academic center was associated with worse survival. Surgical management of both the primary site and evaluation of regional lymph nodes provides a survival advantage. The use of immunotherapy for vulvar melanoma has increased over time however its survival benefit may be limited to the setting of advanced disease. Further investigation is needed to improve outcomes for this rare disease and patients with vulvar melanoma should continue to be enrolled on trials investigating immunotherapy agents.

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