Survival time distribution of advanced stage metastatic melanoma among whites and minority populations in Florida, 1996–2010

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Abstract: Differences in genetic profiles and environmental exposure may impact on the prognostic factors of metastatic melanoma with major implications on the survival of minorities with advanced stage disease at presentation. This study determines the impact of the stage at diagnosis, anatomic/primary site or tumor location, grade, and histologic type on overall survival time distribution across racial groups. A dataset of 80,349 non–Hispanic Whites (NHW), HW and African–Americans (AA) stage III and IV metastatic melanoma patients at presentation was obtained from the Florida Cancer Data System. Measures related to the impact of the stage at diagnosis, anatomic/primary site or tumor location, grade, and histologic type on overall survival time distribution across racial groups are reported. Data were analyzed using SAS. Mean time univariate and multivariate survival statistics across races were analyzed using Kaplan–Meir method and the nonparametric log-rank tests were used to test the homogeneity of survival curves. Significant differences in survival time are reported among the races in primary sites, histology, and stage at diagnosis, but not in terms of tumor grade; survival curve distributions were still significantly different even when adjustments were made for age, nodes, lymphatic invasion, and tumor size.

Keywords: metastatic melanoma; prognostic factors; survival time distribution; race/ethnicity

1. Introduction

It is hypothesized that differences in genetic profile and environmental exposure could contribute to poor survival and increased mortality of racial/ethnic groups[1]. These differences may impact on the histologic type, stage, grade, and primary or anatomic location of tumors, with major implications on the survival of patients with metastatic melanoma.

According to the final version of the 2009 American Joint Committee on Cancer (AJCC) Melanoma Staging and Classification, melanoma cases are classified at diagnosis as In Situ (limited to the epidermis), localized invasive, regional spread, and distant spread[2,3]. For Stage I and II melanoma (in patients with localized disease), tumor thickness, mitotic...
rate, and ulceration were the most powerful predictors of survival in multivariate analysis\(^2\), while lymphatic invasion (LI) was an independent prognostic factor that significantly increased the risk of metastasis\(^4\). In patients with Stage III melanoma, Balch et al. reported that tumor burden or nodal metastasis was the most significant independent predictor of survival in Stage III disease, regardless of whether the patients had micro- or macro-metastasis\(^2\). For distant (Stage IV) metastasis, the site(s) of distant metastasis, the number of metastatic sites and elevated lactate dehydrogenase are the most important predictive factors\(^2\).

Advanced melanoma at presentation in association with poor survival rates among African–Americans (AA) and Hispanics has been the subject of a number of studies\(^1,6-14\). In a retrospective study of metastatic melanoma in AA admitted at the Charity Hospital in New Orleans between 1948 and 1974, Krementz et al.\(^5\) confirmed that disparities exist between AA and Whites with respect to prognosis, the majority of whom presented at advanced stage, with the plantar and palmar surfaces of the feet, hand, toes, and fingers as major sites of origin. Similarly, in an analysis of the California Cancer Registry, Crest and Holly\(^11\) reported that AA and Hispanics are more likely to be diagnosed with acral lentiginous melanoma (ALM) of the lower extremities at a late stage, with poor survival than whites. Furthermore, in a retrospective study of 649 patients (among whom were 36 AA) at the Washington Hospital Center between 1981 and 2000, AA were more likely to be diagnosed with Stage III and IV melanoma (32%) than whites (13%), with a lower survival rate of 59% as compared to that of 85% for Whites\(^10\). Bellows et al.\(^9\) reported that the shorter survival time for AA, as opposed to whites, could neither be attributed to race, age at presentation nor to varying education and poverty levels, but to the stage of the disease at presentation, most of whom presented with ALM. Survival was determined to be inversely related to stage at diagnosis; median survival and 5 year survival were 135 months or 69% versus 45 months or 45% for whites and African–Americans, respectively, with overall survival of 54% versus 36%.

Supporting examples of studies from South Africa also indicate poor prognosis and survival due to the delayed presentation with advanced disease. Hudson et al.\(^16\) studied 85 patients treated retrospectively between 1977 and 1991 and found that significantly more black patients (57%) had advanced metastatic (Stage III and IV) disease compared to patients of mixed ancestry (33%) and White (4%). In another study, Hudson and Krige\(^17\) evaluated 63 black patients for the stage at presentation, tumor site, histologic type, and treatment (among other characteristics). ALM was the most common type with 51% of patients presenting at late Stage (III and IV) metastatic disease, with 5 years survival rate of 25%. Similarly, in studies with data from the SEER program, Merrill et al.\(^14\) reported that Hispanics in the US were more likely to be diagnosed with the more advanced lethal nodular and ALM of the lower extremities than whites. More importantly, recent studies in Florida have confirmed the association between late-stage diagnosis of melanoma in AA and Hispanic as compared to Whites\(^11\), thus underscoring the existing racial disparities in metastatic melanoma survival.

Most researchers studying racial disparities in metastatic melanoma survival have focused on stage at diagnosis as a major predictor. This study extends prior research by analyzing other potential measures of disparities in the survival of metastatic melanoma patients. Thus, the purpose of this study was to determine the impact of the stage at diagnosis, anatomic/primary site or tumor location, grade and histologic type on overall survival time distribution among non–hispanic whites (NHW), HW, and AA.

2. Methods

The Florida Cancer Data System (FCDS) database was accessed to identify White, African–American and Hispanic patients with metastatic melanoma at presentation. A password protected full compact disk was obtained of cases reported to the FCDS from 1996–2010, including an Acquisition Manual and Data Dictionary for code identification and reference. The dataset contained 80,349 patients diagnosed with metastatic melanoma in Florida (1996–2010) and born between 1890 and 2003. The dataset was completely devoid of patient identifiable information, so no consent or ethical issues had to be addressed. The study protocol was reviewed and approved by the Florida Department of Health Institutional Review Board and the Florida Bureau of Epidemiology. A research agreement was signed by the authors in compliance with disclosure limitations, as stipulated by the statute governing the FCDS.

Sampling was done in two stages as follows: (1) Stages III and IV patients with nodal and systemic metastasis for anatomic, histologic, and stage comparisons. Thus, Stages I and II patients and those with unknown race, gender, and sex (i.e. 33,843) were excluded, leaving a total of 46,506 patients. (2) Second, we selected for tumor grade as an indicator of survival. Only 796 patients had reported tumor grades; grade is a recent additional variable collected by the registry.

Melanoma cases of primary origin were identified using morphology codes (C440–C449) of the International Classification of Diseases for Oncology, ICD–0–3\(^13\); and categorized by histologic subtype as superficial spreading, lentigo maligna, acral lentiginous, nodular, etc. However, the SEER staging system was used instead of the clinically relevant revised staging system for melanoma introduced in the sixth edition of the AJCC cancer staging manual (now used by cancer registries) for patients to ensure consistency in staging. The SEER stages were Stages III and IV that were described as localized (confined to
primary site), regional (spread to regional lymph nodes) and distant (cancer had metastasized), plus unknown (i.e., Un–staged)\(^{[19]}\).

Measures related to the impact of the stage at diagnosis, anatomic/primary site or tumor location, grade and histologic type on overall survival time distribution across racial groups are reported. For determination of above measures, race/ethnicity was defined as NHW for all Whites, African–American (AA) all who identified as black and HW for all Hispanics.

2.1. Statistical analysis

Data were analyzed using the Statistical Analysis Software SAS version 9.4.; SAS Institute, Cary, North Carolina. Meantime univariate and multivariate survival statistics across races were analyzed using Kaplan–Meir method and the nonparametric log-rank tests were used to test the homogeneity of survival curves. Kaplan–Meir survival curves were determined from the time of diagnosis of the primary tumor, and considered censored if the actual survival time was not observed; or uncensored if the event was known to have occurred, in which case survival time was observed. Chi-square test was used to test the association between different measures across racial groups at a significant value of \(P < 0.05\). Only anatomic Stage III and IV patients with nodal and systemic metastasis, respectively, and the first incident cases of melanoma were included for comparison by anatomic site, histologic type, and stage at diagnosis as patients may develop more than one primary melanoma. Cases of unknown race, age, and gender are excluded from the analysis. The forward stepwise sequence method was used in reporting significant effects of defined measures on survival time. Our main outcome of interest was overall survival time distribution after a diagnosis of melanoma as primary cancer. To examine temporal trends in survival, we stratified survival time by race into 3 time periods (1992–1995, 1996–1998, and 1999–2001).

3. Results

3.1. Survival time distribution across races

The mean overall time to survival across races is reported in Table 1. Meantime to survival across races were not comparable. Meantime to survival for AA (\(M = 39.47\) months) was less than mean time to survival for NHW (\(M = 49.24\) months) or HW (\(M = 41.01\) months). Meanwhile, the median time to survival distribution for the entire sample data across NHW, AA, and HW [Table 1] showed that NHW reported median time to the survival of 68.7 months, AA reported 78.2 months, whereas HW reported a relatively low median time to the survival of 54.97 months. Log-rank test of the homogeneity of survival curves across all three races indicated that median survival time distribution was not the same for all three races (\(\chi^2 = 22.6, P < 0.001\)). Similar results were obtained for survival time distribution for the three 5-year periods: 1996–2000, 2001–2005, and 2006–2010, respectively, with log-rank test for each time period reporting \(P < 0.05\) (F. Bebe unpublished data, June 2017). However, the overall survival curves by race [Figure 1] shows that there was no significant difference in survival after 120 months.

<p>| Table 1. Mean overall and median time to survival (months) across race categories for patients diagnosed with metastatic melanoma in Florida, 1996–2010 |</p>
<table>
<thead>
<tr>
<th>Race</th>
<th>n</th>
<th>Mean±SD</th>
<th>Median time to survival</th>
<th>Log Rank ((\chi^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHW</td>
<td>44,693</td>
<td>49.24±50.38</td>
<td>68.67</td>
<td>22.6, (P &lt; 0.001)</td>
</tr>
<tr>
<td>AA</td>
<td>274</td>
<td>39.47±44.96</td>
<td>78.20</td>
<td></td>
</tr>
<tr>
<td>HW</td>
<td>1,539</td>
<td>41.01±47.21</td>
<td>54.97</td>
<td></td>
</tr>
</tbody>
</table>

NHW: Non–Hispanic Whites, SD: Standard deviation, AA: African–Americans, HW: Hispanic Whites

3.2. Survival time distribution across primary sites and grades

Survival time distributions were compared across primary sites ranging from C440 to C449 [Table 2 and Figure 2]. Table 2 reports median time to survival distribution across primary sites. Median survival time ranged from a minimum of 59.30 to a maximum of 102.867 months with C449 primary site reporting the highest median survival time and C447 reporting the least median survival time of 59.30 months. Results of the log-rank test indicated that survival curve distribution was not the same across primary sites (\(\chi^2 = 502.024, P < 0.001\)).

Survival time distributions were also compared across grades ranging from Grade 1 to Grade 4 [Table 3], whereas Figure 3 gives the survival time curves across grades reported. Median time to survival ranged from minimum of 57.17 to 87.77 months with Grade 4 reporting the highest median survival time and Grade 1 reporting the least median survival time of 57.17 months. Results of the log-rank test showed that the survival curve distribution was the same across primary sites (\(\chi^2 = 5.8, P < 0.124\)), indicating that Grade did not affect the survival time.

3.3. Survival time distribution across histology type and stage at diagnosis

Survival time distributions were compared across histology type in Table 4. Median survival time ranged from minimum of 51.4 months for histology type 8743 to a maximum of 87.47 months for histology type 8730. Results of the log-rank test indicated that survival curve distribution was not the same across histologic types (\(\chi^2 = 434.9, P < 0.001\)). Thus, histology type significantly affected the survival time.

Survival time distributions were also compared across metastatic melanoma stages: Local, regional, and distant.
Figure 1. Survival curves for non–Hispanic whites (HW) African Americans and HW. No significant difference after 120 months.

Figure 2. Survival curves for primary sites diagnosed.

Figure 3. Survival curves for tumor grades.
Table 2. Survival time across sites of primary cancer for patients diagnosed with metastatic melanoma in Florida, 1996–2010

<table>
<thead>
<tr>
<th>Skin site codes</th>
<th>Total</th>
<th>Failed</th>
<th>Censored</th>
<th>Median time to survival</th>
<th>Log rank ($\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C440</td>
<td>103</td>
<td>52</td>
<td>51</td>
<td>86.933</td>
<td>502.024</td>
</tr>
<tr>
<td>C441</td>
<td>223</td>
<td>120</td>
<td>103</td>
<td>93.000</td>
<td></td>
</tr>
<tr>
<td>C442</td>
<td>1,252</td>
<td>677</td>
<td>575</td>
<td>78.533</td>
<td></td>
</tr>
<tr>
<td>C443</td>
<td>4,527</td>
<td>2,379</td>
<td>2,148</td>
<td>82.167</td>
<td></td>
</tr>
<tr>
<td>C444</td>
<td>3,644</td>
<td>1,882</td>
<td>1,762</td>
<td>78.233</td>
<td></td>
</tr>
<tr>
<td>C445</td>
<td>14,753</td>
<td>9,948</td>
<td>4,805</td>
<td>63.833</td>
<td></td>
</tr>
<tr>
<td>C446</td>
<td>11,858</td>
<td>7,764</td>
<td>4,094</td>
<td>65.067</td>
<td></td>
</tr>
<tr>
<td>C447</td>
<td>8,017</td>
<td>5,529</td>
<td>2,488</td>
<td>59.300</td>
<td></td>
</tr>
<tr>
<td>C448</td>
<td>55</td>
<td>29</td>
<td>26</td>
<td>75.233</td>
<td></td>
</tr>
<tr>
<td>C449</td>
<td>2,074</td>
<td>391</td>
<td>1,683</td>
<td>102.867</td>
<td></td>
</tr>
</tbody>
</table>

C440 lip, C441 eyelid, C442 eye and external canal, C443 face, C444 scalp and neck, C445 trunk, C446 upper limb and shoulder, C447 upper limb and lip, C448 Overlapping lesion of skin, C449 not otherwise specified.

Table 3. Survival time across tumor grades for patients diagnosed with metastatic melanoma in Florida, 1996–2010

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total</th>
<th>Uncensored</th>
<th>Censored</th>
<th>Median time to survival</th>
<th>Log–rank ($\chi^2$)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>134</td>
<td>77</td>
<td>57</td>
<td>57.167</td>
<td>5.8</td>
<td>0.124</td>
</tr>
<tr>
<td>2</td>
<td>168</td>
<td>101</td>
<td>67</td>
<td>81.733</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>346</td>
<td>117</td>
<td>229</td>
<td>79.033</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>52</td>
<td>96</td>
<td>87.767</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grade: 1 - Well differentiated, 2 - Moderately (intermediate) differentiated, 3 - Poorly differentiated, 4 - Undifferentiated

Table 4. Survival time across selected histology types for patients diagnosed with metastatic melanoma in Florida, 1996–2010

<table>
<thead>
<tr>
<th>Type</th>
<th>Total</th>
<th>Uncensored</th>
<th>Censored</th>
<th>Median time to survival</th>
<th>Log rank ($\chi^2$)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>8720</td>
<td>29,299</td>
<td>17,957</td>
<td>11,342</td>
<td>69.70</td>
<td>434.9</td>
<td>0.001</td>
</tr>
<tr>
<td>8721</td>
<td>3,707</td>
<td>1,765</td>
<td>1,942</td>
<td>77.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8723</td>
<td>197</td>
<td>133</td>
<td>64</td>
<td>60.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8730</td>
<td>249</td>
<td>113</td>
<td>136</td>
<td>87.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8742</td>
<td>968</td>
<td>1,125</td>
<td>843</td>
<td>82.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8743</td>
<td>8,497</td>
<td>6,287</td>
<td>2,210</td>
<td>51.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8744</td>
<td>533</td>
<td>293</td>
<td>240</td>
<td>73.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8745</td>
<td>804</td>
<td>428</td>
<td>376</td>
<td>75.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8771</td>
<td>204</td>
<td>117</td>
<td>87</td>
<td>66.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8772</td>
<td>697</td>
<td>312</td>
<td>385</td>
<td>87.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Histologic type: 8720 - Malignant melanoma (unspecified), 8721 - Nodular melanoma, 8723 - Halo nevus malignant melanoma, 8730 - Amelanotic melanoma, 8742 - Lentigo maligna melanoma, 8743 - Superficial spreading melanoma, 8744 - Acral lentiginous melanoma, 8745 - Desmoplastic melanoma, 8771 - Epithelioid cell melanoma, 8772 - Spindle cell melanoma (unspecified).

[Table 5]; whereas Figure 4 reports the survival curve for the three categories of stage. Median survival time for three category disease stages ranged from minimum of 64.3 months to 105.2 months. Results of the log-rank test indicated that survival curve distribution was not the same across stages ($\chi^2 = 619.9, P < 0.001$).

3.4. Survival time distribution across race adjusted for age, nodes, LI, and tumor size

Median survival time distribution was compared across race adjusting for the effect of age and number of nodes affected, age and the number of lymphatic items, age, and tumor size (Table 6 and Figure 5). Median survival time across races adjusting for the effect of age and number of nodes affected, age and the number of lymphatic items, age and tumor size ranged from minimum of 54.97 months (HW) to 78.20 months (AA). Results of the log-rank test indicated that survival curve distribution was not the same across racial groups ($\chi^2 = 22.6, P < 0.001$) as the forward stepwise sequence method reported all variables age, nodes, LI and tumor size included in the model had a significant effect on survival time distribution. A closer look at the survival curve for all three races [Figure 5].
Table 5. Survival times across stages for patients diagnosed with metastatic melanoma in Florida, 1996–2010

<table>
<thead>
<tr>
<th>Stage</th>
<th>Total</th>
<th>Uncensored</th>
<th>Censored</th>
<th>Median time to survival</th>
<th>Log–rank ($\chi^2$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>38,619</td>
<td>26,259</td>
<td>12,360</td>
<td>64.33</td>
<td>619.90</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Regional</td>
<td>5,219</td>
<td>2,190</td>
<td>3,029</td>
<td>77.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant</td>
<td>2,668</td>
<td>322</td>
<td>2,346</td>
<td>105.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Survival times across race adjusting for effect of age, nodes, lymphatic invasion, and tumor size

<table>
<thead>
<tr>
<th>Race</th>
<th>Total</th>
<th>Uncensored</th>
<th>Censored</th>
<th>Median time to survival</th>
<th>Log–rank ($\chi^2$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHW</td>
<td>44,693</td>
<td>27,689</td>
<td>17,004</td>
<td>68.67</td>
<td>22.6</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>AA</td>
<td>274</td>
<td>127</td>
<td>147</td>
<td>78.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HW</td>
<td>1,539</td>
<td>955</td>
<td>584</td>
<td>54.97</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NHW: Non–Hispanic Whites, SD: Standard deviation, AA: African–Americans, HW: Hispanic Whites

Figure 4. Survival curves for stages.

Figure 5. Survival curves for non–Hispanic whites (HW) African Americans and HW, adjusted for age, nodes, lymphatic invasion, and tumor size.
would show that 5 year overall survival was about 54%, 61%, and 47% for NHW, AA, and HW, respectively; no significant difference in survival could be deduced after 10 years (120 months).

4. Discussion

It is well documented that non–white populations have very low incidence rates of metastatic melanoma[29], that the rate is increasing among minorities, and that racial/ethnic differences abound with regard to stage at diagnosis, grade, anatomic, and histologic type distribution of metastatic melanoma[1,6-8,10,21], resulting in lower survival rates compared to Whites. However, few studies have analyzed and compared the differences in survival time distribution of these predictors among NHW, AA and HW populations. In Florida or the United States as a whole. In this study, mean time to survival and median survival time distribution among NHW, AA, and HW were not comparable. There were significant differences in survival time among the races in primary sites, histology, and stage at diagnosis, but not in terms of tumor grade. The survival curve distribution among races was still significantly different when adjustments were made for age, nodes, Linnvasion, and tumor size.

Estimating survival with only 155 metastatic melanoma patients in Rumania, Sandru et al.[25] reported a mean and median overall survival of 9.2 months and 5.3 months, respectively. In one of the few studies on melanoma survival in the United States, Pollack et al.[23] using 10 years of SEER data that included over 68,495 primary cases, found racial/ethnic differences in survival, but not in multivariate analysis. The present study reports only on racial differences using a dataset from the FCDS of over 80,000 patients in which the mean time to survival for AA (39.5 months) was less than that of NHW (49 months) and that of HW (41 months). However, (unlike the meantime to survival) AA registered a higher median survival time ($\chi^2 = 22.6, P = <0.001$) than NHW and HW, probably the result of a comparatively very low incidence rate.

Location of the primary tumor is reported as an independent prognostic factor in the survival of patients with metastatic melanoma[9,24,25]. This study indicates that survival time distribution was not the same across primary or anatomic sites, but no difference was shown in tumor grades. In other words, tumor location affected survival time with the skin of limb and hip, skin of trunk and skin of upper limb and shoulder registering the lowest median time to survival ($P < 0.001$), but not tumor grade ($P < 0.124$). Studies have shown that gender plays an important role in anatomic site impact on survival with the trunk having a poor prognosis compared to other sites[26-29]. However, primary tumor location is said to lose its significance in multivariate analysis[30], or show borderline significance in overall survival analysis[31].

Stage distribution of melanoma at diagnosis impacts patient survival, as distant metastasis often portends a worse prognosis, and this varies substantially by race and histology type[19,30,31]. Studies have shown that the most common histologic type of metastatic melanoma among all racial groups is superficial spreading melanoma (SSM), except African–American for whom ALM is most common[9,11,23,32,33]. One study with a very low percentage of not otherwise stated (NOS) cases (9%) found Lentigo Maligna Melanoma (LMM) as the most common[34], whereas another with a >50% NOS cases and combining both SEER and registry data in the largest ever analysis of minority metastatic melanoma cases reported Hispanics with a higher incidence of ALM than Whites and Blacks, with the rate for Blacks similar to that of Whites[23]. This disparity in histologic type may largely account for survival differences among racial groups. Bellows et al.[9] reported that the shorter survival time for AA as opposed to whites could be attributed to the stage of the disease at presentation, as most of them presented with ALM. In addition, survival was determined to be inversely related to stage at diagnosis; median survival and 5 years survival were 135 months or 69% versus 45 months or 45% for whites and AA, respectively, with overall survival of 54% versus 36%[9].

With greater than a third of the cases NOS, the present study shows (in descending order) that nodular melanoma, LMM, SSM, and ALM were the most important histologic types. The large NOS cases may have further reduced the analytical power of the study, despite the large dataset. However, results showed that histology type significantly affected survival time, as the survival curve distributions were not the same across histologic types. In the present study, only 58% of the MM cases were staged and up to 83% of these as local, whereas 11% and 6% were regional and distant, respectively. Median survival time distribution compared across stages was the highest for regional and distant metastatic stages (77.7 and 105.2, $\chi^2 = 619.9, P < 0.001$). The small number of cases in the regional and distant stages compared to the local stage may be responsible for the longer median survival time, which is contrary to the literature citing worse overall survival for regional and distant metastatic stages[10,23,35].

Age, tumor size, number of nodes, and LI at diagnosis are important prognostic indicators for metastatic melanoma that may impact on survival time distribution across racial groups; and adjusting for these variables may determine their influence on survival disparities. Elderly patients often present with ulcerated and thicker lesions[36,37]. Balch et al.[34] estimated that each decade increase in age is associated with a decline in survival rates. Tumor size or thickness is associated with increased mortality[38], and is influenced by ulceration; the presence of both decreased survival in all metastatic melanoma stages, and as high as 22% in thick (>4.0 mm) tumors[39].

Xu et al.[4] reported LI as an independent prognostic factor that significantly increases the risk of metastatic melanoma in patients in clinical stages I and II whose
prognosis is poorer than those without LI. Patients with LI (primary metastatic melanoma lesions with high densities of lymphatic vessels) have been associated with positive sentinel lymph node biopsy and a worse clinical outcome and reported to have shorter disease-free and overall survival rates\(^{37,39}\). Balch \textit{et al.}\(^{34}\) showed that 49% and 37% of metastatic melanoma patients with nodal metastasis survived 5 years and 10 years, respectively; however, a median time of 7.5 months was reported by Barth \textit{et al.}\(^{36}\) when 1521 patients with distant metastasis were treated. In a recent study to evaluate the differences in overall survival of racial/ethnic groups in the United States, Ward-Peterson \textit{et al.}\(^{35}\) showed that median follow-up time was 81 months and that Blacks had the worst unadjusted survival compared to other races. Bradford \textit{et al.}\(^{39}\) found 5 year and 10 year ALM-specific survival rates at 80% and 68%, respectively, but this result was no longer significant when controlled for tumor thickness.

The present study with over 80,000 patients reports significant differences in median survival time distribution across racial groups even after adjusting for age and nodes, age and tumor size, and age and LI. Survival times ranged from 68 months for NHW, 78 for AA and 55 for HW. This range is much longer than that reported by Balch \textit{et al.}\(^{35}\) and Ward-Peterson \textit{et al.}\(^{35}\), and the median for AA is larger than that of NHW and HW. This is probably because of the large sample size of this study and the very low incidence rate of AA. However, the above authors studied median survival times in general and not disparities in median survival times among racial groups, and hence, their work could not be directly compared to the present one.

4.1. Strengths and limitations

This study draws its strength not only from the availability of this large dataset for studying metastatic melanoma (especially among minorities – AA and HW) but also from the many advantages Florida has in that it is ethnically and racially diverse, with the second highest incidence rate in the United States.\(^{12,18}\) The mean time to survival for AA (39.5 months) was less than that of Whites (49 months) and that of Hispanics (41 months), and this is in agreement with published reports.

The incidence rate for AA and HW patients (5% and 1%, respectively), was too low (compared to NHW) to perform in–depth analysis and may have reduced the statistical power. Not all patients had complete information in their records. Patients with NOS or missing values were excluded from the analysis. Excluding patients with missing values may have introduced bias and further reduced the power of the study. However, due to the size of the dataset and sampling or patient selection procedure of the variables studied, the effect on validity may be minimal. Classification of metastatic melanoma as NOS histologically seems to be a common problem with registry data.

Data on comorbidity (a known factor that impacts on survival) were not available at the FCDS. Thus, comorbidity could not be incorporated as part of the survival analysis, within the time constraints of this study. In this case, linking of cancer registries to vital statistics and hospital discharge records for a one–stop data acquisition process may help reduce bias and increase validity. Furthermore, we did not account for other factors (mitotic rate, ulceration, and serum lactate dehydrogenase), as these were recent additions to the revised edition of the AJCC Melanoma staging and classification\(^{2}\), and not readily available at the FDCS for of the years studied.

5. Conclusion

The fact that the incidence of MM has been steadily increasing creates an urgent need for research on minorities with metastatic melanoma, despite the low incidence in this population group. Few studies have analyzed and compared the differences in survival time distributions of metastatic melanoma predictors among NHW, AA, and HW populations in Florida or the United States as a whole. This may be the first study to look at the survival distribution of major predictors of MM in Florida using a huge dataset of over 8000 patients statewide. In this study, mean time to survival and median survival time distribution among NHW, AA, and HW were not comparable. It was shown that significant differences in survival time exist among the races in primary sites, histology, and stage at diagnosis, but not in terms of tumor grade; and that survival curve distributions among the races were still significantly different even when adjustments were made for age, nodes, LI, and tumor size.

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