Trends in short-term survival from distant-stage cutaneous melanoma in the United States, 2001-2013 (CONCORD-3)

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Abstract

Background

Survival from metastatic cutaneous melanoma is substantially lower than for localised disease. Treatments for metastatic melanoma have been limited, but remarkable clinical improvements have been reported in clinical trials in the last decade. We described the characteristics of US patients diagnosed with cutaneous melanoma during 2001-2013 and assessed trends in short-term survival for distant-stage disease.

Methods

Trends in 1-year net survival were estimated using the Pohar Perme estimator, controlling for background mortality with life tables of all-cause mortality rates by county of residence, single year of age, sex and race for each year 2001-2013. We fitted a flexible parametric survival model on the log-hazard scale to estimate the effect of race on the hazard of death due to melanoma, and estimated 1-year net survival by race.

Results

Only 4.4% of the 425,915 melanomas were diagnosed at a distant stage, with higher proportions in men, older patients and African Americans. Age-standardised 1-year net survival for distant-stage disease was stable at around 43% during 2001-2010. From 2010 onwards, survival improved rapidly, reaching 58.9% (95% confidence interval [CI] = 56.6% to 61.2%) for patients diagnosed in 2013. Younger patients experienced the largest improvement. Survival for distant-stage disease increased in both Blacks and Whites, but was consistently lower in Blacks.

Conclusions

One-year survival for distant-stage melanoma improved during 2001-2013, particularly in younger patients and those diagnosed since 2010. This improvement may be a consequence of the introduction of immune-checkpoint-inhibitors and other targeted treatments for metastatic and unresectable disease. Persistent survival inequalities exist between Blacks and Whites, suggesting differential access to treatment.
The incidence of cutaneous melanoma has been rising in most Caucasian populations over the past 50 years. In the United States, the age-standardised incidence rate rose from 8 per 100,000 person-years in 1975 to 25 in 2016. Cutaneous melanoma was the 4th and 5th most common cancer in men and women, respectively, in the US in 2016, with a total of 82,476 new cases.

The third cycle of the CONCORD programme for the global surveillance of cancer survival (CONCORD-3) highlighted increasing trends in age-standardised 5-year net survival from cutaneous melanoma in most countries during 2000-2014; 5-year net survival exceeded 90% for patients diagnosed during 2010-2014 in the United States, Australia, New Zealand and most Nordic and Western European countries, but was below 60% in Ecuador, China and Taiwan. Stage at diagnosis is an important predictor of prognosis, and survival for disease diagnosed at an advanced stage is much lower than for localised disease. If detected at a localised stage (Tumour Node Metastasis Stage I-II and resectable Stage III), cutaneous melanoma can be surgically treated with a favourable outcome. Five-year relative survival for localised melanoma of the skin diagnosed in the last 20 years was higher than 90% in Germany, Denmark, Estonia, Sweden, and the United States.

Until about 2010, when advanced disease (TNM stage III unresectable melanoma and stage IV disease) was mainly treated with chemotherapy (e.g. dacarbazine) and cytokines (e.g. interleukin-2), the prognosis for metastatic melanoma was generally poor, with survival as low as 16% at 5 years after diagnosis for patients diagnosed in the US. In recent years, major improvements in treatment, involving the use of targeted therapies and immunotherapy, have led to unprecedented clinical benefit. Ipilimumab, the first immunotherapy, and vemurafenib, the first targeted treatment for metastatic and unresectable melanoma, were approved by the US Food and Drug Administration (FDA) in 2011.

The aim of this study is to describe the characteristics of patients diagnosed with cutaneous melanoma during 2001-2013, using data provided by 34 US population-based...
cancer registries included in CONCORD-3, and to assess trends in short-term (1-year) survival for distant-stage disease.

Methods

CONCORD-3 obtained anonymised individual tumour records from 322 population-based cancer registries in 71 countries worldwide, for patients who had been diagnosed with one of 18 common cancers, including melanoma, during 2000-2014 and followed up to 31 December 2014. Data acquisition, ethical approval and data quality control for the CONCORD programme have been described elsewhere.\(^4\) Cancer registries submitted records on all patients diagnosed with a melanoma, defined by morphology codes in the range 8720-8790 in the International Classification of Diseases for Oncology, third revision [ICD-O-3].\(^{11}\) We restricted survival analysis to malignant melanoma (ICD-O-3 behaviour code 3) arising in the skin (ICD-O-3 topography codes C44.0-C44.9), including the skin of the labia majora (C51.0), vulva (C51.9), penis (C60.9), and scrotum (C63.2).

Records with incomplete data, or for tumours that were benign, in situ, of uncertain behaviour, metastatic from another organ, or unknown if primary or metastatic, or on patients with age outside the range 15-99 years, were considered ineligible for analysis.

We excluded tumours registered only from a death certificate or discovered at autopsy, since their duration of survival was unknown, as well as records for which the vital status or sex was unknown, and those with an invalid date or sequence of dates.

We included in analysis only primary, invasive, malignant cutaneous melanoma. If two or more invasive primary malignant melanomas were detected in the same person but with different dates of diagnosis, the record with the earliest date of diagnosis was retained. Registry data sets in which 15.0% or more of patients were lost to follow-up were excluded from the survival analyses.

Patients diagnosed in 2014 were included in CONCORD-3 but were not included in this study, because a full year of follow-up was not available by the study closure date (31 December 2014). To assess trends in survival for the same registries, we retained only
registries that submitted data on patients diagnosed up to and including 2013, with follow-up to 31 December 2014.

The CONCORD protocol required information on stage of disease at the time of diagnosis for patients diagnosed from 2001 onward, because the completeness of data on stage in many countries and US states was known to be much lower before 2001.

Stage was categorised as localised, regional and distant, according to the SEER Summary Stage 2000 classification.12 “Distant stage” includes melanoma with distant lymph node involvement, metastatic skin lesions, further contiguous extension or metastasis to other organs. Age at diagnosis was grouped into 15-44, 45-54, 55-64, 65-74 and 75-99 years. Race was categorised as White, Black and other race/ethnicities (Asian/Pacific Islander; American Indian/Alaska Native; other, unspecified or unknown race).

Melanomas were defined by morphology (ICD-O-3 8720–8790). We selected melanomas of the skin on the basis of topographic codes C44.0-C44.9 (skin), C51.0 (including the skin of the labia majora), C51.9 (vulva), C60.9 (penis) or C63.2 (scrotum). Melanomas were further categorised by anatomic subsite as arising in the skin of the head and neck (C44.0-C44.4), the trunk (C44.5), the limbs (C44.6-C44.7) or the genital organs (C51.0, C51.9, C60.9, C63.2), or as lesions overlapping two of those categories, or of the skin with anatomic location not otherwise specified (C44.8-C44.9). Histological sub-types were grouped according to the first revision of ICD-O-3,11 as malignant melanoma, not otherwise specified (NOS, 8720), superficial spreading (8743), lentigo maligna (8742), nodular (8721), acral (8744) and all other morphologies (8722-8723, 8726-8727, 8730, 8740-8741, 8743, 8745-8746, 8750, 8760-8761, 8770-8774, 8780, 8790).

We explored the distribution of stage at diagnosis by sex, age, race, topography and morphology. Survival analyses were restricted to patients diagnosed with distant-stage melanoma. One-year net survival for patients diagnosed in each of the 13 years 2001-2013 was estimated with the non-parametric Pohar Perme estimator,13 using the STATA14 command strns.15 Net survival is the cumulative probability that cancer patients survive their cancer up to a given time since diagnosis (e.g. 1 year), after correcting for other causes of
death (background mortality). To control for background mortality, which varies by geographical area, demographic characteristics and over time, we used life tables of all-cause mortality in the general population by single year of age, sex, single calendar year, race (Blacks, Whites and others) and county within each state. These life tables were kindly provided by the National Cancer Institute.16

We estimated trends in one-year net survival for five age groups. We then obtained age-standardised estimates for all ages combined, using the second of the three sets of International Cancer Survival Standard weights (0.28, 0.17, 0.21, 0.20 and 0.14), designed for cancers with broadly constant incidence by age.17 Survival was estimated for men and women, and for both sexes combined.

We fitted a flexible parametric survival model on the log-hazard scale, to estimate the effect of race on the hazard of death due to distant-stage melanoma; excess mortality and net survival by race were also estimated,18 with race as a categorical variable. Restricted cubic splines for the effect of age at diagnosis (3 degrees of freedom) and year of diagnosis (4 degrees of freedom) were included with the command rcsgen,19 including time-dependent effects.

Results

The CONCORD database included individual records for 1,040,814 adults (15-99 years) diagnosed with a primary, malignant cutaneous melanoma in 41 state-wide cancer registries in the US, covering a total population of 257 million people (80.2% of the US population). Data quality was generally high. The proportion of patients excluded for incomplete dates or for other reasons ranged from 0.0 to 4.4% (Table 1). Overall, 36.0% of patients were diagnosed with an in situ tumour.

Of the 632,861 patients eligible for inclusion in survival analyses, we excluded 3,045 (0.5%) because the cancer was registered only from a death certificate or discovered at autopsy; survival time for these patients is unknown. Only 2.7% of the remaining 629,816 patients were lost to follow-up or censored within 5 years from diagnosis, but this proportion
was much lower among patients with distant-stage disease (0.3%). The diagnosis was histologically confirmed in 99.3% of tumours (data not shown).

New Jersey was excluded because of the high proportion of patients lost to follow-up (48.2%). A further 118,239 patients were excluded from six state-wide registries (Arkansas, California, Massachusetts, Oklahoma, Tennessee and Washington), because data were not available for patients diagnosed up to and including 2013. Finally, we explored the distribution of 425,915 patients by sex, age, race, topography, morphology and stage at diagnosis.

Most patients diagnosed during 2001-2013 were men (56.8%), and they were generally older than women (median age at diagnosis: 64 vs. 57 years, respectively). Only 0.6% of patients were Black (Table 2). Data on stage at diagnosis were available for 386,885 (90.8%) patients.

Seventy-seven percent (77.1%) of patients were diagnosed with localised disease. This proportion was stable over time (76.4%-79.8%, data not shown), slightly higher in women (79.3% vs. 75.3%) and in younger patients (79.7% vs. 74.1% in patients aged 15-44 and 75-99 years, respectively). Four percent (4.4%) of melanomas were diagnosed at a distant stage, with a slightly higher proportion in men than women (4.6% vs. 2.8% respectively, in 2001; 6.2% vs. 4.5% in 2013, data not shown). Fifteen percent (14.6%) of Blacks were diagnosed with distant-stage disease, compared to only 4.4% in Whites and 1.2% in the “other race” category. Patients with distant-stage melanoma were generally older (median age: 65 years) than those diagnosed with localised (61 years) or regional (62 years) disease (data not shown).

Melanomas arose mostly on the skin of the limbs (42.1%), the trunk (32.1%) and the head and neck (20.6%) and were diagnosed at a distant stage in 2.0% of those cases (Table 2). Melanomas arising in overlapping or unspecified locations only accounted for 4.9% of all cases, but half of these (49.6%) were diagnosed at an advanced stage. The proportion of melanomas registered with an unspecified morphology was 51.9%, followed by superficial spreading (29.8%) and nodular melanoma (7.2%). Distant-stage melanomas represented
less than 1% of the superficial spreading and lentigo maligna morphologies (0.8% and 0.6%, respectively), but up to 6.7% of those classified as malignant melanoma, NOS.

We restricted survival analysis to 18,601 patients diagnosed with distant-stage disease (Figure 1). In 2001, age-standardised 1-year net survival was 42.8% (95% CI 39.3% to 46.3%) and remained stable until 2010 (Table 3). Survival improved rapidly from 2010 onwards, reaching 58.9% (95% CI = 56.6% to 61.2%) for patients diagnosed in 2013. The trend was similar for men and women, although survival was slightly but consistently higher in women (Table 3).

One-year net survival increased for all ages (Figure 2, Table 3). The youngest patients (15-44 years) experienced the largest absolute improvement, particularly from 2010, rising from 44.4% (95% CI = 35.9% to 52.8%) in 2001 to 67.8% (95% CI = 62.0% to 73.6%) in 2013. For patients aged 45-54 years, one-year survival increased from 45.7% (95% CI = 38.4% to 53.1%) in 2001 to 62.7% (95% CI = 57.6% to 67.8%) in 2013. We observed similar trends in patients aged 55-64 and 65-74 years, starting from 2011; both survival curves reached 56% (56.1%, 95% CI = 51.6% to 60.6%; and 56.7%, 95% CI = 52.4% to 60.9%, respectively) in 2013. One-year survival for patients aged 75 years or more remained at 44.5% (95% CI = 39.9% to 49.1%) or lower throughout the period 2001-2013.

Age-standardised 1-year net survival increased for both Whites and Blacks with distant-stage melanoma (Figure 3). Survival for Whites rose from 42.3% (95% CI = 39.9 to 44.8%) in 2001 to 56.1% (95% CI = 54.6% to 57.6%) in 2013. Among Blacks, 1-year survival improved from 37.0% (95% CI = 32.0% to 42.7%) to 50.7% (95% CI = 46.3% to 55.7%) over the same period. The excess hazard of death due to melanoma within one year of diagnosis was 13% higher in Blacks than Whites (excess hazard ratio = 1.13, 95% CI = 1.00 to 1.27; data not shown).

Discussion

This study includes data from 34 state-wide cancer registries, covering 56.9% of the US population, and is the largest population-based analysis to date of trends in 1-year
survival for distant-stage cutaneous melanoma. It shows a dramatic improvement in survival, particularly between 2010 and 2013.

The proportion of melanomas diagnosed at a distant stage remained stable over time (4-5%) and was slightly lower in women than men. Sex inequalities in stage at diagnosis are well known, they are commonly attributed to differences in health-seeking behaviour. Traditionally, women tend to visit their health-care provider and perform skin checks more frequently than men; this can translate to a higher proportion of women being diagnosed with localised disease.

Blacks were more likely to be diagnosed with distant-stage melanoma than Whites. The perception among African Americans that melanoma risk is low is considered a major cause for delayed diagnosis. Consistent with previous studies, patients diagnosed at a distant stage were generally older.

One-year net survival improved noticeably for men and women, and in both Blacks and Whites. This improvement may reflect the recent introduction of new treatments for metastatic and unresectable disease.

The first immune checkpoint inhibitor approved by the FDA, in March 2011, ipilimumab, showed one-year overall survival for patients diagnosed with metastatic melanoma in a phase III randomized clinical trial as high as 45.6%, compared with less than 30% (25.3%) for patients treated with standard therapy.

Vemurafenib, the first licensed targeted treatment for patients with metastatic disease and the BRAF V600E mutation, was also shown to increase short-term survival. A phase III randomized trial of 675 patients diagnosed with metastatic melanoma showed an overall 6-month survival of 84% (95% CI = 78% to 89%) in those treated with vemurafenib compared to 64% (95% CI = 56% to 73%) in those treated with dacarbazine. The FDA approved the drug on this evidence in August 2011.

Our study has shown a substantial improvement in short-term survival since 2010-11 for patients diagnosed with distant-stage melanoma of the skin, particularly for younger patients. Most of the improvement occurred from 2010, one year before FDA approval of the
new lines of treatment. Some of these patients may have been recruited to clinical trials, which started well before 2010. Additionally, they may have received the newer treatments through the FDA expanded access programs, which provide access to investigational drugs before their official approval to patients with life-threatening conditions who cannot be enrolled in clinical trials.

Data on whether the patients were recruited to a clinical trial or received systemic therapy for compassionate use were not available to us to explore these hypotheses. However, a population-based study of the impact of targeted and immune-based therapies for metastatic or unresectable melanoma in Ontario found that about 5% of patients were already being treated with the new therapies in 2007; this percentage increased to more than 82% by 2015. That study confirmed the use of immunotherapy well before the approval of ipilimumab by Health Canada in 2012, and highlighted its widespread use in recent years. A similar study in the US showed that the use of immunotherapy in patients under 65 years improved rapidly after 2010, from 8-12% during 2004-2010 to 30% in 2014.

Patients aged 75 years or more with distant-stage disease experienced considerably less improvement in short-term survival. This may be due to less frequent use of the newer therapies. A recent study designed to identify factors associated with the treatment of metastatic melanoma in the US found that older patients were less likely to receive ipilimumab or to be tested for the BRAF mutation. This may have resulted from concerns about how they would tolerate the new treatments. Previous studies on solid tumours have shown that age can act as a barrier to receipt of optimal treatment, due to a higher prevalence of comorbidity, or absence of data on treatment efficacy from clinical trials, and more frequent adverse effects. A US study showed that only 46% of patients aged 80 years or more received imatinib, a highly effective treatment for chronic myeloid leukaemia, compared with 89.7% of those aged 20-59 years.

The CONCORD-3 study protocol did not require detailed information on specific types of treatment, so it was not possible to estimate the proportion of patients who received immune-checkpoint inhibitors or targeted treatments. Data on socio-economic status and
type of health insurance were not collected. That information might have helped to explain the disparities in the stage distribution and stage-specific survival by age and race. An analysis of 61,650 melanoma patients aged 18-64 years diagnosed in the United States during 2007-2012 estimated that the proportion of patients with metastatic disease ranged from only 3.7% in the non-Medicaid insurance group to 15.5% among Medicaid and 10.7% among uninsured patients. A recent systematic review of the cost-effectiveness of immune-checkpoint inhibitors in the US estimated that the individual cost of treatment for metastatic melanoma ranged from US$152,000 to US$303,000 for a patient with a median survival time. The cost of targeted therapies for metastatic melanoma with the BRAF V600E mutation was estimated at between US$149,000 and US$319,000. Recent analyses have shown that patients were less likely to receive immunotherapy if they had no insurance or only Medicaid coverage, received a lower income, or received care at a community practice rather than an academic centre. Such differences in access to treatment may partly explain the racial disparities in the recent trends in short-term survival reported in this study.

One-year net survival was consistently lower in Blacks than Whites. Survival was not estimated for other races. The proportion of patients lost to follow-up, including those whose deaths are missed by the cancer registries, is generally higher among Asian/Pacific Islanders (API) than Whites and Blacks. Incomplete follow-up among API and other minority groups may lead to over-estimation of survival and biased comparisons.

Several studies have shown a survival disadvantage for Blacks diagnosed with melanoma in the US. A study of more than 260,000 people diagnosed during 1988-2011 estimated an absolute gap of almost 20% (89% vs. 70%) between Blacks and Whites in 5-year relative survival for all stages combined. Among Whites and Blacks of non-Hispanic origin, the difference in 5-year overall survival was almost 30% (82% vs. 53%) during 1982-2011.

Racial disparities in survival from melanoma have commonly been ascribed to a less favourable stage distribution of black patients. However, we have shown that while the proportion of distant-stage melanoma was higher among Blacks than Whites, one-year...
survival for distant-stage melanoma was also consistently lower among Blacks than among Whites. This gap in survival suggests racial differences in treatment and access to care.

Despite the exclusion of about 2,500 patients registered with a distant-stage melanoma in cancer registries for which incidence data were not complete for 2001-2013, we were nevertheless able to include 18,601 patients: this is the largest population-based analysis of trends in one-year net survival for distant-stage disease.

In conclusion, this is the first population-based study to show a recent improvement in short-term survival from distant-stage cutaneous melanoma in the United States. This may be due to the availability of new and more effective therapies for the treatment of metastatic or unresectable disease. The dramatic improvement since 2010 in short-term survival for melanoma of the skin diagnosed at the metastatic or unresectable stage is important, because for most other solid tumours, survival for metastatic disease has not changed for several decades.\textsuperscript{54-56} More detailed population-based studies would help evaluate access to novel treatments, and their longer-term survival benefit for patients diagnosed with distant-stage melanoma.

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DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared because they are personal data, provided in anonymized form by participating US cancer registries to the CONCORD programme under relevant ethical and statutory approvals in the US and the UK, to protect the privacy of individuals. Requests for data should be addressed to the registry or registries concerned.

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Table 1: Data quality indicators, patients diagnosed with malignant melanoma of the skin during 2000-2014 in the United States

| US registries | Calendar period | No. of patients submitted | Ineligible, % | No. of eligible patients | Excluded, % | No. of patients included | Data quality indicators, % |
|---------------|----------------|--------------------------|--------------|-------------------------|------------|--------------------------|---------------------------|
|               |                |                          | Incomplete dates | In situ | Other | DCO | Other | Lost to follow-up | Censored |
| All US registries | 2000-2014 | 1,040,814 | 0.6 | 36.0 | 2.6 | 632,861 | 0.5 | 0.0 | 629,816 | 2.6 | 0.1 |
| Alabama       | 2000-2014     | 23,564               | 0.9 | 41.3 | 2.3 | 13,084 | 0.6 | 0.0 | 13,012 | 0.0 | 0.0 |
| Alaska        | 2000-2013     | 1,533                | 4.4 | 30.6 | 3.5 | 944 | 0.4 | 0.0 | 940 | 0.0 | 0.0 |
| Arkansas      | 2000-2011     | 7,592                | 0.3 | 31.9 | 3.3 | 4,897 | 0.3 | 0.0 | 4,879 | 0.0 | 0.0 |
| California    | 2000-2011     | 127,043              | 1.1 | 36.9 | 2.3 | 75,851 | 0.2 | 0.0 | 75,712 | 0.0 | 0.0 |
| Colorado      | 2000-2013     | 21,135               | 0.3 | 33.1 | 3.1 | 13,427 | 0.7 | 0.0 | 13,338 | 0.0 | 0.0 |
| Connecticut   | 2000-2014     | 21,602               | 0.4 | 40.9 | 2.2 | 12,211 | 0.2 | 0.0 | 12,185 | 5.5 | 0.0 |
| Delaware      | 2000-2014     | 6,283                | 0.2 | 44.0 | 1.4 | 3,413 | 0.2 | 0.0 | 3,406 | 0.0 | 0.0 |
| Florida       | 2000-2013     | 89,847               | 0.1 | 35.4 | 2.7 | 55,590 | 0.7 | 0.1 | 55,134 | 0.0 | 0.0 |
| Georgia       | 2000-2014     | 43,981               | 0.0 | 35.6 | 2.0 | 27,451 | 0.4 | 0.0 | 27,350 | 0.0 | 0.0 |
| Hawaii        | 2000-2014     | 5,753                | 0.3 | 33.7 | 1.5 | 3,710 | 0.2 | 0.0 | 3,704 | 7.5 | 0.0 |
| Idaho         | 2000-2014     | 9,032                | 0.6 | 40.8 | 2.2 | 5,095 | 0.7 | 0.0 | 5,059 | 0.0 | 0.0 |
| Indiana       | 2000-2014     | 25,599               | 0.6 | 32.3 | 3.3 | 16,347 | 0.5 | 0.0 | 16,269 | 0.0 | 0.0 |
| Iowa          | 2000-2014     | 15,612               | 0.6 | 32.6 | 3.7 | 9,846 | 0.2 | 0.0 | 9,822 | 2.8 | 0.0 |
| Kentucky      | 2000-2014     | 23,097               | 0.0 | 33.3 | 2.8 | 14,764 | 0.2 | 0.0 | 14,729 | 6.4 | 0.0 |
| Louisiana     | 2000-2014     | 25,599               | 0.6 | 32.6 | 3.3 | 16,347 | 0.5 | 0.0 | 16,269 | 0.0 | 0.0 |
| Maine         | 2000-2013     | 7,860                | 0.3 | 38.4 | 3.0 | 4,581 | 0.3 | 0.0 | 4,565 | 0.0 | 0.0 |
| Maryland      | 2000-2014     | 29,516               | 0.4 | 40.2 | 1.8 | 16,981 | 0.6 | 0.1 | 16,868 | 0.0 | 0.0 |
| Massachusetts | 2000-2009     | 23,194               | 0.0 | 34.5 | 3.0 | 14,483 | 0.4 | 0.0 | 14,420 | 0.0 | 0.0 |
| Michigan      | 2000-2013     | 41,986               | 0.2 | 36.5 | 2.5 | 25,505 | 0.6 | 0.0 | 25,335 | 0.0 | 0.0 |
| Minnesota     | 2000-2013     | 27,449               | 0.0 | 38.1 | 1.9 | 16,472 | 0.3 | 0.0 | 16,421 | 0.0 | 0.0 |
| Mississippi   | 2002-2014     | 9,214                | 0.8 | 31.6 | 2.8 | 5,968 | 0.6 | 0.0 | 5,931 | 0.0 | 0.0 |
| Montana       | 2000-2014     | 5,595                | 0.6 | 37.8 | 2.9 | 3,289 | 0.5 | 0.0 | 3,272 | 0.0 | 0.0 |
| Nebraska      | 2000-2014     | 7,894                | 0.6 | 33.4 | 3.5 | 4,930 | 0.5 | 0.0 | 4,906 | 0.0 | 0.0 |
| State                  | Period     | Cases | Age 1 | Age 2 | Age 3 | Age 4 | Cases | Age 1 | Age 2 | Age 3 | Age 4 | Cases | Age 1 | Age 2 | Age 3 | Age 4 |
|-----------------------|------------|-------|--------|--------|--------|--------|-------|--------|--------|--------|--------|-------|--------|--------|--------|--------|
| New Hampshire         | 2000-2014  | 9,727 | 0.1    | 40.3   | 2.3    | 5,575  | 0.3   | 0.0    | 5,560  | 0.0    | 0.0    |
| New Jersey            | 2000-2014  | 49,568| 0.8    | 42.7   | 1.9    | 27,024 | 0.4   | 0.0    | 26,910 | 48.2   | 0.0    |
| New Mexico            | 2000-2014  | 8,720 | 0.0    | 40.1   | 2.2    | 5,030  | 0.6   | 0.0    | 5,000  | 8.7    | 0.4    |
| North Carolina        | 2000-2014  | 47,654| 0.0    | 39.5   | 2.4    | 27,727 | 0.4   | 0.0    | 27,602 | 0.0    | 0.0    |
| Ohio                  | 2000-2014  | 54,382| 0.1    | 35.7   | 3.0    | 33,292 | 0.6   | 0.0    | 33,079 | 0.0    | 0.0    |
| Oklahoma              | 2000-2010  | 9,135 | 0.4    | 24.8   | 3.9    | 6,479  | 1.1   | 0.0    | 6,407  | 0.0    | 0.0    |
| Oregon                | 2000-2013  | 24,301| 0.1    | 40.9   | 2.6    | 13,703 | 0.5   | 0.0    | 13,637 | 0.0    | 0.0    |
| Pennsylvania          | 2000-2014  | 62,912| 0.4    | 39.0   | 2.4    | 3,703  | 0.4   | 0.0    | 3,688  | 0.0    | 0.0    |
| Rhode Island          | 2000-2014  | 6,363 | 0.4    | 39.0   | 2.4    | 3,703  | 0.4   | 0.0    | 3,688  | 0.0    | 0.0    |
| South Carolina        | 2000-2014  | 24,940| 0.0    | 40.8   | 1.8    | 14,309 | 0.5   | 0.0    | 14,230 | 0.0    | 0.0    |
| Tennessee             | 2000-2011  | 19,264| 0.5    | 28.5   | 3.3    | 13,047 | 0.3   | 0.0    | 13,003 | 0.0    | 0.0    |
| Texas                 | 2000-2013  | 59,374| 0.9    | 28.4   | 3.5    | 39,882 | 0.8   | 0.0    | 39,555 | 0.0    | 0.0    |
| Utah                  | 2000-2014  | 14,946| 0.1    | 38.2   | 2.1    | 8,893  | 0.1   | 0.0    | 8,885  | 0.0    | 0.2    |
| Vermont               | 2000-2013  | 4,537 | 0.1    | 38.8   | 1.9    | 2,688  | 0.3   | 0.0    | 2,679  | 0.0    | 0.0    |
| Washington            | 2000-2008  | 22,317| 0.8    | 39.2   | 2.2    | 12,876 | 0.2   | 0.0    | 12,843 | 0.0    | 0.0    |
| West Virginia         | 2000-2014  | 8,894 | 1.3    | 31.1   | 3.4    | 5,707  | 0.4   | 0.0    | 5,682  | 0.0    | 0.0    |
| Wisconsin             | 2000-2013  | 21,636| 0.9    | 28.4   | 3.6    | 14,507 | 1.0   | 0.0    | 14,366 | 0.0    | 0.0    |
| Wyoming               | 2000-2013  | 2,658 | 0.2    | 38.6   | 2.9    | 1,548  | 0.1   | 0.0    | 1,547  | 0.0    | 0.1    |

a Incomplete dates: records in which the year of birth is unknown; or the month and/or year of diagnosis is unknown; or the year of last known vital status is unknown. Other: records with incomplete data, or for tumours that are benign (behaviour code 0), of uncertain behaviour (1), metastatic from another organ (6), or unknown if primary or metastatic (9); or for patients with age outside the range 15-99.

b Other: vital status or sex unknown; invalid date or sequence of dates.

c Censored: patients whose last known vital status is "alive" and who were censored within five years of diagnosis or, if diagnosed in 2010 or later, before 31 December 2014.
Table 2: Adults (15-99 years) diagnosed with primary malignant melanoma of the skin during 2001-2013 in 34 US registries: distribution (no., %) by sex, age at diagnosis, race, anatomic location, morphology and SEER \(^a\) Summary Stage 2000

| Patients’ and tumour characteristics | Localised | Regional | Distant | Unknown | Total |
|--------------------------------------|-----------|----------|---------|---------|-------|
|                                      | No. (%)   | No. (%)  | No. (%) | No. (%) | No. (%) |
| **Sex**                              |           |          |         |         |       |
| Men                                  | 182,150 (75.3) | 24,747 (10.2) | 12,443 (5.1) | 22,470 (9.4) | 241,810 (56.8) |
| Women                                | 146,022 (79.3) | 15,365 (8.3) | 6,158 (3.3) | 16,560 (9.1) | 184,105 (43.2) |
| **Age group, years**                 |           |          |         |         |       |
| 15-44                                | 61,321 (79.7) | 7,039 (9.1) | 2,074 (2.7) | 6,510 (8.5) | 76,944 (18.1) |
| 45-54                                | 58,041 (78.2) | 6,857 (9.2) | 2,942 (4.0) | 6,386 (8.6) | 74,226 (17.4) |
| 55-64                                | 69,434 (77.4) | 8,296 (9.2) | 4,131 (4.6) | 7,848 (8.8) | 89,709 (21.1) |
| 65-74                                | 66,251 (76.8) | 7,739 (9.0) | 4,204 (4.9) | 8,116 (9.3) | 86,310 (20.3) |
| 75-99                                | 73,125 (74.1) | 10,181 (10.3) | 5,250 (5.3) | 10,170 (10.3) | 98,726 (23.2) |
| **Race**                             |           |          |         |         |       |
| White                                | 315,166 (77.3) | 39,200 (9.6) | 18,052 (4.4) | 35,550 (8.7) | 407,968 (95.8) |
| Black                                | 1,286 (51.8) | 500 (20.1) | 363 (14.6) | 333 (13.5) | 2,482 (0.6) |
| Other                                | 11,720 (75.8) | 412 (2.7) | 186 (1.2) | 3,147 (20.3) | 15,465 (3.6) |
| **Anatomic location**                |           |          |         |         |       |
| Head and neck                        | 67,980 (77.6) | 9,140 (10.4) | 2,036 (2.3) | 8,405 (9.7) | 87,561 (20.6) |
| Trunk                                | 111,247 (81.3) | 12,071 (8.8) | 2,817 (2.1) | 10,754 (7.8) | 136,889 (32.1) |
| Limbs                                | 146,001 (81.5) | 16,259 (9.1) | 3,314 (1.9) | 13,561 (7.5) | 179,135 (41.1) |
| Overlapping region or NOS\(^b\)      | 2,014 (9.7) | 2,297 (11.0) | 10,321 (49.6) | 6,191 (29.7) | 20,823 (4.9) |
| Skin of genital organs               | 930 (61.7) | 345 (22.9) | 113 (7.5) | 119 (7.9) | 1,507 (0.4) |
| **Morphology**                       |           |          |         |         |       |
| Malignant melanoma, NOS\(^b\)       | 156,892 (1.8) | 17,992 (8.2) | 14,538 (6.7) | 29,031 (13.3) | 225,635 (51.9) |
| Superficial spreading                | 115,022 (89.0) | 7,906 (6.1) | 1,077 (0.8) | 5,285 (4.1) | 129,782 (29.8) |
| Lentigo maligna                      | 23,590 (88.0) | 808 (3.0) | 162 (0.6) | 2,258 (8.4) | 27,163 (6.2) |
| Nodular                              | 19,161 (62.1) | 8,963 (29.1) | 1,653 (5.4) | 1,064 (3.4) | 31,329 (7.2) |
|                | Count (Percentage) |
|----------------|-------------------|
| Acral lentiginous | 2,990 (68.2)      |
|                 | 1,017 (23.2)      |
|                 | 189 (4.3)         |
|                 | 186 (4.3)         |
|                 | 4,428 (1.0)       |
| Others          | 10,517 (65.2)     |
|                 | 3,426 (21.2)      |
|                 | 982 (6.1)         |
|                 | 1,206 (7.5)       |
|                 | 16,518 (3.8)      |
| Total           | 328,172 (77.1)    |
|                 | 40,112 (9.4)      |
|                 | 18,601 (4.4)      |
|                 | 39,030 (9.1)      |
|                 | 425,915 (100.0)   |

*a* SEER: Surveillance, Epidemiology and End Results

*b* NOS: not otherwise specified
Table 3: Number of patients at risk (No.) together with age-standardised and age-specific 1-year net survival (NS, %) for patients diagnosed with distant-stage cutaneous melanoma during 2001-2013 in 34 US registries, by sex and age at diagnosis

| Calendar year | US registries | Sex          | Age, years |
|---------------|---------------|--------------|------------|
|               |               | Men (No.)    | 15-44 (No.) | 45-54 (No.) | 55-64 (No.) | 65-74 (No.) | 75-99 (No.) |
| 2001          | 921           | 42.8 (39.3 to 46.3) | 626 (39.9 to 44.1) | 295 (48.7 to 54.9) | 132 (44.4 to 52.8) | 178 (45.7 to 53.1) | 169 (50.2 to 57.8) | 198 (32.7 to 39.4) | 244 (39.7 to 46.3) |
| 2002          | 1,009         | 38.5 (35.2 to 41.7) | 673 (36.8 to 40.7) | 336 (41.6 to 47.2) | 162 (46.4 to 54.0) | 186 (34 to 40.8) | 198 (37.3 to 44.0) | 208 (36.1 to 42.7) | 255 (33.2 to 39.3) |
| 2003          | 1,070         | 44.1 (40.7 to 47.4) | 733 (42.3 to 46.3) | 337 (48 to 53.9) | 133 (49.7 to 58.2) | 185 (44.5 to 51.7) | 230 (45.3 to 51.7) | 244 (42.8 to 49.2) | 278 (32.3 to 38.1) |
| 2004          | 1,226         | 42.9 (39.8 to 46.0) | 807 (40 to 43.9) | 419 (48.6 to 53.8) | 163 (46.7 to 54.3) | 207 (38.8 to 45.4) | 250 (42.4 to 48.6) | 256 (42.9 to 49.1) | 350 (40.8 to 46.3) |
| 2005          | 1,244         | 42.8 (39.6 to 46.0) | 855 (42.5 to 46.4) | 389 (43.2 to 48.7) | 137 (43.9 to 52.1) | 195 (44.3 to 51.3) | 266 (45.4 to 51.4) | 288 (40.5 to 47.2) | 358 (38.5 to 43.9) |
| 2006          | 1,359         | 45.6 (42.5 to 48.7) | 879 (44 to 47.8) | 480 (48.5 to 53.7) | 146 (51.5 to 59.5) | 232 (47.6 to 54.0) | 312 (44.4 to 49.9) | 297 (41.7 to 47.4) | 372 (38.7 to 44.0) |
| 2007          | 1,319         | 44.5 (41.3 to 7.7) | 855 (44.2 to 48.2) | 464 (45.6 to 50.8) | 130 (45.5 to 50.5) | 209 (43.7 to 50.5) | 281 (45.3 to 51.1) | 317 (48.4 to 51.4) | 382 (37 to 42.1) |
| 2008          | 1,381         | 42.8 (39.7 to 45.9) | 935 (41.1 to 45.0) | 446 (46.6 to 51.8) | 142 (43 to 51.1) | 225 (47.2 to 53.7) | 336 (40.3 to 45.5) | 290 (45.2 to 51.0) | 388 (37.2 to 42.3) |
| 2009          | 1,486         | 42 (39.1 to 45.0) | 988 (40.5 to 44.1) | 498 (45 to 49.9) | 159 (44.7 to 52.4) | 230 (38.9 to 45.2) | 346 (43.2 to 48.4) | 341 (38.4 to 49.2) | 410 (36.2 to 41.2) |
| 2010          | 1,678         | 45.7 (43.0 to 48.3) | 1,151 (44.5 to 47.8) | 527 (47.8 to 52.5) | 207 (50.7 to 63.8) | 277 (46.1 to 51.9) | 385 (41.4 to 46.4) | 366 (41.4 to 46.4) | 443 (34.9 to 39.6) |
| 2011          | 1,725         | 51.9 (49.2 to 54.6) | 1,168 (45.4 to 52.6) | 557 (56.8 to 61.1) | 168 (61.1 to 73.2) | 246 (51.7 to 57.8) | 430 (45.8 to 50.5) | 388 (47.4 to 52.4) | 474 (39.3 to 44.0) |
| 2012          | 2,012         | 56.7 (54.3 to 59.2) | 1,355 (54.6 to 57.7) | 657 (60.3 to 64.1) | 226 (70.3 to 76.3) | 297 (58.2 to 63.8) | 485 (51 to 55.5) | 486 (51.1 to 55.7) | 518 (44.5 to 49.1) |
| Year | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 | Value 6 | Value 7 |
|------|--------|--------|--------|--------|--------|--------|--------|
| 2013 | 2,171  | 58.9   | (56.6 to 61.2) | 1,418  | 57.4   | (54.4 to 60.5) | 753    | 61.4   | (57.7 to 65.1) | 251    | 67.8   | (62.0 to 73.6) | 349    | 62.7   | (57.6 to 67.8) | 484    | 56.1   | (51.6 to 60.6) | 541    | 56.7   | (52.4 to 60.9) | 546    | 43.9   | (39.4 to 48.3) |

*a CI: confidence interval*
Figure titles and legends

**Figure 1.** Patients included in survival analysis

**Figure 2.** Trends in age-specific 1-year net survival (%) for patients diagnosed with distant-stage cutaneous melanoma during 2001-2013 in the United States

**Figure 3.** Trends in age-standardised 1-year net survival (%) for patients diagnosed with distant-stage cutaneous melanoma during 2001-2013 in the United States, by race
Figure 1

629,816

Patients diagnosed in 2000 and 2014 excluded

567,765

Include only registries with all incidence years 2001-2013

449,526

Exclude registries with proportion of lost to follow up higher than 15.0%

425,915

Exclude localised, regional and unknown stage

18,601
Figure 2

- **All ages**
- 15–44
- 45–54
- 55–64
- 65–74
- 75–99

Net survival (%) by year of diagnosis for different age groups from 2001 to 2013.
