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REVIEW

Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe – a systematic review of the literature

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Background: Given the increasing incidence in cutaneous malignant melanoma (CMM) and the recent changes in the treatment landscape, it is important to understand stage-specific overall and recurrence-free survival patterns in Europe. Despite publications such as EUROCARE-5, there is limited information on stage-specific survival for CMM in Europe.

Method: We carried out a systematic literature review to provide an up-to-date summary of stage-specific survival and recurrence-free survival patterns in patients with CMM in Europe. Studies were included if they were published in Medline during the past 12 years and included information on stage-specific survival and/or recurrence in CMM.

Results: Of the 8,749 studies identified, 26 studies were included, representing nine countries. Collectively, the studies covered a population of 152,422 patients and included data from 1978 to 2011. Randomized clinical trials and single-center observational studies comprised the most common study designs, including five large registry-based studies. Stage-specific information for survival and recurrence varied: 5-year overall survival: 95%–100% (stage I), 65%–92.8% (stage II), 41%–71% (stage III), and 9%–28% (stage IV); 5-year relapse-free survival was reported less frequently: 56% (stage II), and 28%–44% (stage III). Studies reporting survival by sentinel node (SN) status reported 5-year overall survival as 80%–95% for negative SN (stage I/II) and 35%–75% for positive SN (stage III) status; recurrence-free survival at 5 years: 76%–90% for negative and 35%–58% for positive SN status. Some studies included comparisons of survival by key patient sociodemographic characteristics, suggesting that these have a substantial influence on survival and recurrence estimates.

Conclusion: The studies identified in this review show large variations in stage-specific overall and recurrence-free survival by study type and by country. Owing to differing study designs and populations, it is difficult to make detailed comparisons. Large population-based studies that include stage-specific survival and recurrence in Europe are therefore important.

Keywords: cutaneous malignant melanoma, cancer, survival, recurrence, Europe, stage

Introduction

Cutaneous malignant melanoma (CMM) is the ninth most common cancer in Europe, with an annual incidence of 13.5 new cases per 100,000 population and over 100,000 new cases diagnosed in 2012 (3% of total cancers).[1]

With a steady increasing trend in annual incidence rates,[2] the incidence of CMM is increasing more rapidly than that of any other cancer in Europe – apart from lung cancer in women.[3] Large differences in CMM incidence and mortality exist between European countries, with the highest estimated age-standardized incidence of CMM reported in Switzerland for men and in Denmark for women. Central and Eastern

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European countries have the lowest reported incidence rates in Europe. A total of 22,211 deaths due to CMM were estimated in Europe in 2012, with annual CMM mortality rates per 100,000 population ranging between 0.5 (Albania) and 3.6 (Norway).[1] It has been suggested that some of the differences in CMM incidence and mortality may be due to missed opportunities for early diagnosis and incomplete reporting of CMM.[4]

In cancer, early detection alone may not necessarily lead to good survival rates; however, CMM is an example in which early detection is associated with higher cure rates.[5] There is known variation in reported 5-year survival by country and region in Europe. EUROCARE-5[6] analyzed data from more than 10 million patients with cancer diagnosed up to 2007 with follow-up until 2008. Five-year relative survival for CMM was 83.2%, which has not improved since EUROCARE-4.[7,8] EUROCARE-5 reports variation in 5-year relative survival by region, with best survival rates in northern and central Europe (87.7% and 87.6%, respectively) compared to 82.6% in southern Europe and 74.3% in Eastern Europe. This variation may be due to later stage at diagnosis and differences in treatment regimes.[6,9]

Despite attempts to collect and consolidate information in various databases, there are limited published data on stage-specific survival in Europe. Although surgery remains the definitive treatment for patients with earlier-stage CMM (stage I–III), there has been an increase in the use of newly approved drugs for systemic treatment of patients with unresectable and stage IV disease. However, since these novel therapies were introduced relatively recently, it is unlikely that they have influenced survival rates presented in this study. Until recently, interferon 2α remained the only approved systemic adjuvant therapy for patients with stage IIB–III CMM and has minimal effect on patient overall survival (OS). Ipilimumab as adjuvant therapy has now been shown to improve progression-free survival (PFS) in patients with radically resected stage III CMM and is approved in the USA for this indication.[10] Ipilimumab is a monoclonal antibody approved for first- and second-line treatment of advanced CMM since 2011; it typically achieves response rates of 5%–15% in patients with regional and distant metastases[11] and is associated with long-term survival in approximately 20% of patients.[12] In patients with BRAF V600E (or the rarer V600K) mutated stage IV CMM, the BRAF inhibitors vemurafenib and dabrafenib have demonstrated response rates of approximately 50%.[13] Encouragingly, treatment of advanced CMM continues to evolve, with new agents now targeting the programmed death ligand–receptor interaction, such as the anti-PD1 antibodies pembrolizumab and nivolumab, and also targeted drugs that can be used in combination with BRAF inhibitors to inhibit the MAP-kinase pathway, such as the MEK inhibitors trametinib and cobimetinib.[14,15]

Given the increasing incidence of all-stages CMM and changes in the treatment landscape, it is important to understand the stage-specific survival and recurrence-free survival patterns in Europe from contemporary data and review the reported variation. Reporting stage-specific survival is of importance as the overall CMM survival data may be confounded by an increase over time in proportions of patients diagnosed with early-stage disease (stage I) and a change in staging because of implementation of sentinel node (SN) procedure.[16]

We carried out a systematic review with the objective to evaluate published robust data on stage-specific survival as well as recurrence-free survival by stage in patients with CMM in Europe.

Materials and methods

Search strategy and study inclusion criteria

We developed and followed a standard protocol for this review according to the PRISMA guidelines for systematic reviews, which define a rigorous process of study identification, screening, eligibility, and inclusion (Table S1).[17] Studies were considered eligible for inclusion in this review if they were published during the past 12 years (period of publication from January 1, 2004 to December 31, 2015). All included studies were published in English. To ensure study quality, only those published in national or international peer-reviewed journals were considered. Studies were considered for inclusion only if they reported stage-specific rates of survival and/or recurrence in adult (≥18 years of age) patients with CMM. In order to include only studies with more robust outcome data with stage-specific information, studies with fewer than 400 patients were excluded. The cutoff of 400 patients per study was reached after initial review of studies, which showed that the quality of smaller studies was poorer and included mainly single-institution retrospective studies. With only a small proportion of patients in the advanced and metastatic setting in these publications, the accuracy of survival reported and follow-up time recorded in smaller studies was seen to be of poor quality and not relevant to this review paper. Also excluded were reviews, meta-analyses, and case reports.

Study identification and data extraction were performed by searching the Medline scientific literature database using the following search terms: "melanoma", "skin

cancer", "survival", "mortality", "recurrence", "metastatic", "metastases" (full search terms provided in Table S2). In addition, relevant references and bibliographies were manually searched by trained researchers for additional studies. An initial review of titles and abstracts, and subsequently, a full review of all remaining search results were carried out independently by two reviewers to determine whether they met the criteria for inclusion in this review (Figure S1). All disagreements were resolved via review by a third reviewer.

Data extraction and synthesis

From each of the identified studies, the following information was extracted: author name(s), date of publication, date/period of coverage of study, study country/countries, description of study population, demographic information, follow-up duration, overall and stage-specific survival, and overall and stage-specific recurrence-free survival rate. Additional information of interest for the particular study was also noted, including potential sources of confounding and whether any sensitivity analyses were performed. In studies where rates were provided for various years, only the most recent estimates were included.

All extracted information was synthesized with the overall interpretation of the findings, taking into account potential sources of study heterogeneity, demographic background of CMM patients, follow-up duration, and potential sources of confounding.

Results

A total of 8,749 studies were identified from the Medline database search, of which 26 studies were included. The studies included populations from nine countries (Denmark, Finland, France, Germany, Italy, the Netherlands, Poland, Sweden, and the United Kingdom), with the majority of studies being from northern Europe (Table 1).[18–43] Collectively, the identified studies covered a population of 152,422 European patients. We included 5 large population-based registry studies[18–20,42,43] (Table 2), 7 randomized clinical trials (RCTs)[21–27] (Table 3), and 14 observational studies[28–41] (Table 4). The 26 identified studies collectively included data on CMM patients from 1978 to 2011. Overall, across countries and by study type, stage-specific information for survival and recurrence varied: 5-year OS: 95%–100% (stage I), 65%–92.8% (stage II), 41%–71% (stage III), and 9%–28% (stage IV); 5-year relapse-free survival (RFS) was reported less frequently: 56% (stage II) and 28%–44% (stage III). Studies reporting survival by SN status reported 5-year OS as 80%–95% for negative SN (stage I/II) and 35%–75% for positive SN (stage III) status; recurrence-free survival at 5 years was 76%–90% for negative and 35%–58% for positive SN status.

Pooling the survival data from population registry studies, RCTs, and observational studies provides a wide variation in the survival and recurrence data. We have presented these data by study type in Tables 2–4.

Although the staging system used by studies included in this review was not always clearly stated, most studies used the staging system of the American Joint Committee on Cancer (AJCC) or the corresponding Union for International Cancer Control (UICC) staging system.

Five population registries with large patient cohorts were identified from Denmark,[43] Germany,[18] Sweden,[19,42] and the Netherlands.[20] The Danish study included 27,010 patients; the German study, 37,155 patients; the two Swedish studies, 5,915 and 27,235 patients; and the Dutch registry, 33,181 patients (Table 2). Although the primary purpose of the Dutch publication was to study outcomes from CMM of unknown primary origin, only 2.6% of patients (n=857) fell into this category. No significant difference existed between the two groups of patients (CMM of known primary and unknown primary) reporting a 5-year survival of 55% for

Table 1 Number of included studies by country and key study characteristics

Country	Number of studies	Number of patients (range of patients)	Number of patients (across studies)	Time-period covered (range of years)
Multi-country studies[22–27]	6	444–1,388	5,709	1988–2004
Italy[33–37]	5	1,108–2,954	8,060	1980–2009
Germany[18,30–32]	4	697–37,155	41,193	1978–2007
Poland[38,39]	2	459–1,207	1,666	1994–2007
Sweden[19,42]	2	5,915–27,235	33,150	1990–2011
The Netherlands[20,40]	2	429–33,181	33,610	1995–2009
UK[21,41]	2	472–674	1,146	1995–2003
Denmark[43]	1	27,010	27,010	1989–2011
Finland[28]	1	423	423	2002–2009
France[29]	1	455	455	1999–2004
Total	26	423–37,155	152,422	1978–2011

Table 2 Five-year stage-specific survival from five large population-based registry studies (Denmark, Germany, Sweden, and the Netherlands)

Country	Study	Registry coverage	Study period	Population (N and stage)	Survival analysis type	5-year survival
Denmark	Bay et al[43]	National coverage	1989–2011	27,010 patients (all stages)	Relative survival, age-adjusted	All stages: 90% (women) 82% (men) Stage I: 95%–98% Stage II: 78%–89% Stage III: 59%–71% Stage IV: 13%–25%
Germany	Eisemann et al[18]	11 cancer registries (33 million people, 40% of German population)	1997–2006	37,155 patients (all stages)	Relative survival, age-adjusted	All stages:[d] 91.9% (women) 87.0% (men) Stage IV (n=1,117): 18.2%–28.2%[a]
Sweden	Eriksson et al[19]	National coverage	1990–2007	27,235 patients (all stages); 609 stage III and 196 stage IV	Crude disease-specific survival (Kaplan–Meier)	Stage I: 97.3% (97.0%–97.5%)[b] Stage II: 72.5% (71.2%–73.8%) Stage III: 41.3% (37.0%–45.5%) Stage IV: 17.8% (12.3%–24.1%)
Sweden	Plym et al[42]	Uppsala/Örebro region (2 million people, 21% of Swedish population)	1997–2011	5,915 patients (all stages)	Relative survival, age-adjusted	Stage I: 97.7%–100% Stage II: 69.0%–92.8% Stage III: 44.7%–59.0%
The Netherlands	de Waal et al[20]	National coverage	2003–2009	33,181 patients (all stages), (1,689 stage III and 286 stage IV)	Crude all-cause survival (Kaplan–Meier)	Stage III: 54.6% (51.3%–57.9%)[c] Stage IV: 8.9% (4.5%–13.3%)

Notes: Results in each study report the range of DSS by various patient groups (ie, education, age, and disease severity).[a]Study reports survival data only by T, N, or M classification, making a precise estimate for stages I, II, and III impossible since a low T stage can be node-positive (and thus stage III). The exception for this is M1 disease (stage IV). [b]J Lyth, Regional Cancer Center, Linköping, Sweden, personal communication, March, 2015. [c]Data is merged from patients with melanoma of unknown primary and melanoma with known primary origin. Five-year survival (95% CI) for stage III with macroscopic disease, one lymph node involved was 50.1% (43%–57.3%), for stage III macroscopic disease and more than one positive lymph node was 27.1% (20.7%–33.5%). Five-year survival (95% CI) for stage IV, subcutaneous or distant lymph nodes was 35.3% (17.5%–53%), for stage IV, with lung metastasis was 5.4% (0%–15.3%), and for stage IV with metastasis to other distant sites was 1.5% (1.2%–4.1%). [d]Overall stage-specific results are not provided, only for each separate age, sex, and socioeconomic deprivation group.
Abbreviations: CI, confidence interval; DSS, disease-specific survival.

stage III and 9% for stage IV.[20] The first Swedish study is a comprehensive nationwide study of the survival pattern of CMM. The primary purpose of this study was to report the association of level of education with stage at diagnosis and survival in CMM, and this study reported poorer survival in those with lower level of education.[19] For this review, we obtained results from study authors (J Lyth, Regional Cancer Center, Linköping, Sweden, personal communication, March, 2015), with 5-year survival reported as 41.3% (95% confidence interval 37.0%–45.5%) for stage III disease and 17.8% (12.3%–24.1%) for stage IV disease. The second Swedish study extracts information from an extensive population-based register covering a population of 2 million people. The main objective of this study was to compare the epidemiological data, management, and outcome of CMM between the younger and the older patient population. Results presented show a significant difference between these two groups of patients regarding all the aspects mentioned earlier, with younger patients having better survival rates.[42] The German registry study of CMM covers 40% of the total German population. Results are reported as age-adjusted relative survival by TNM classification, and we estimated the stage IV age-adjusted relative survival to be 18%–28% at 5 years.[18] Finally, the Danish population-based register study included 27,010 CMM patients diagnosed between 1989 and 2011 with the aim to investigate the trends in incidence and in survival of CMM in Denmark. The study found that the incidence of CMM in Denmark had more than doubled over the 23-year study period, with the increase seen mainly in lower stage groups and superficial spreading CMM. Age-standardized relative OS had increased in recent years for both men and women.[43]

We included seven RCTs (Table 3) that reported survival using Kaplan–Meier methodology and recurrence rates from 4 to 8 years. Six RCTs compared outcomes in patients with CMM with stage IIB–III or stage III disease using interferon alfa 2a or 2b as the investigational treatment arm. The number of patients included ranged from 444[24] to 1,388 patients.[23] The results show some differences in long-term OS and some improvement in RFS in patients treated with interferon.[23,24,26]

Table 3 Stage-specific survival rate and recurrence-free survival rate in CMM patients from seven randomized controlled trials (at 5 years unless reported otherwise)

Country	Study	Clinical trial design	Study period	Population (N and stage)	Stage-specific overall survival for both treatment arms	Stage-specific RFS in both treatment arms
UK	Hancock et al[21]	Interferon alfa 2a versus no further treatment in radically resected melanoma	1995–2000	674 patients (stage IIB/III)	Stage IIB/III: 44% (both groups)	Stage IIB/III: 32% (both groups)
Multi-country	Kleeberg et al[22]	Interferon α versus interferon γ versus mistletoe extract versus observation after surgery in patients with either thickness >3 mm or regional lymph node metastasis	1988–1996	830 patients (stage IIB/III)	Stage IIB: 55%[a] approximately (all groups) Stage III: 35%[a] approximately (all groups) Stage IIB and III: 40% at 8 years	Stage IIB: 39.3% (all groups) Stage III: 27.6% (all groups) Stage IIB/III: 32.4% (RFS at 8 years)
Multi-country	Eggermont et al[23]	Intermediate doses of interferon alfa 2b versus observation	1996–2000	1,388 patients (stage IIB/III)	All Stage IIB and III: 50.2%; 47.7% (observation); 48.3% and 53.1% interferon groups Stage IIB: 66.0% (all) Stage III N1: 55.5% (all) Stage III N2: 39.4% (all) at 4.5 years	All Stage IIB and III: 43.3%; 40% (observation); 42.3% and 46.1% (interferon groups) Stage IIB: 59.5% (all) Stage III N1: 51.4% (all) Stage III N2: 31.0% (all)[b]
Multi-country	Garbe et al[24]	Interferon alfa 2a plus or minus dacarbazine versus surgery alone in patients with regional lymph nodes metastases	1997–2001	444 patients (stage III)	Stage III: 42.4% surgery; 59% (interferon) 45.2% (interferon + dacarbazine)[c]	Stage III: 27.3% surgery; 39% (interferon); 29.4% (interferon + dacarbazine) (RFS at 4 years)
Multi-country	Eggermont et al[25]	Interferon alfa 2b versus observation in resected stage III melanoma	2000–2003	1,256 patients (stage III)	Stage III: 46.4% (observation) and 47.8% (interferon); 1 positive LN: 61.4% (observation) and 64.3% (interferon); >1 positive LN: 40.5% (observation) and 48.5% (interferon) at 7 years	Stage III 34.6% (observation) and 39.1% (interferon), 1 positive LN: 46.8% (observation) and 52.3% (interferon); >1 positive LN: 26.9% (observation) and 35.5% (interferon) (RFS at 7 years)
Multi-country	Hansson et al[26]	Two different durations of adjuvant therapy with intermediate-dose interferon alfa 2b in patients with high-risk melanoma	1996–2004	855 patients (stage IIB/IIC/III)	Stage IIB/III: 56.1 months median survival in control group; 72.1 and 64.3 months in treatment groups. Median follow-up time 72.4 months	Stage IIB/III: 23.2 months median RFS; 37.8 and 28.6 months in treatment arms
Multi-country	Gillgren et al[27]	2 cm versus 4 cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm	1992–2004	936 patients (stage II)	Stage II: 65% (both groups)	Stage II: 56% (both groups)

Notes: Survival reported is Kaplan–Meier overall survival. [a]Data were extracted from figures. [b]This study has reported distant metastases-free survival at 4.5 years, not RFS. [c]This study has reported disease-specific survival at 4 years and not overall survival.
Abbreviations: CMM, cutaneous malignant melanoma; LN, lymph node; RFS, recurrence-free survival

Survival varied from approximately 35%–50%[21,23–26] in control groups to approximately 50%–60% for those treated with interferon for stage IIB/III patients.[23–26] The recurrence-/RFS rate in stage IIB/III patients reported at 5 years was approximately 30%[21,22] overall; in stage III patients, the rate was approximately 30%–35% for those patients not treated with interferon, and was 40%–45% for those treated with interferon.[24,25] As these studies report recurrence-free survival rates in different groups, further comparisons are difficult to make. Gillgren et al[27] presented results comparing 2 versus 4 cm excision margins on survival for 936 patients with stage II CMM and reported OS to be 65% at 5 years, and stage-specific rate of recurrence to be 56%.

Table 4 provides a summary of 14 observational studies: four retrospective and 10 prospective studies, including one from a CMM university registry[31] that reported 13 years of follow-up. The range of median follow-up in the prospective studies was from 3 years[38] to more than 18 years[36].

Table 4 Five-year stage-specific survival and recurrence-free survival rate reported in 14 observational studies

Country	Study	Study period	Study type and length of follow-up (if recorded)	Study description	Population and stage at diagnosis	5-year stage-specific survival (DSS or OS) according to SN status	5-year stage-specific RFS according to SN status
Finland	Koskivuo et al[28]	2000–2009	Two-center retrospective. Median follow-up 2.5 years	SN biopsy and survival in patients ≥70 years	423 patients (stage I–II)	Stage I–II: 88.6% Stage III: 46% (DSS)	Stage I–II: 80% Stage III: 39%
France	Debarbieux et al[29]	1999–2004	Single-center retrospective. Mean follow-up 29 months	SN biopsy and completion lymph node dissection and prognosis	455 patients (stage IB/II)	Stage I–II: 95%[a] approximately Stage III: 60%[a] approximately (DSS)	Stage I–II: 80%[a] approximately Stage III: 40%[a] approximately
Germany	Kunte et al[30]	1996–2007	Single-center retrospective	Prognostic factors associated with SN positivity and effect of SN status on survival	854 patients (stage I–II)	Stage I–II: 91.1% Stage III: 69.1% (DSS)	Stage I–II: 90.1% Stage III: 58.1%
Germany	Hohnheiser et al[31]	1978–1997	Single-center registry prospective. Median follow-up 13 years	Factors that influence time to recurrence and survival after first recurrence	2,487 patients (stage I/II, III)	Stage I/II: 80%[a] approximately Stage III: 40%[a] approximately (OS)	N/R
Germany	Meier et al[32]	2000–2006	Single-center retrospective. Mean follow-up 49.5 months	Comparison of classification systems in melanoma SNs	697 patients (stage IB/II)	Stage I–II: 85%–90%[a] approximately (OS)	Stage I–II: 85%[a] approximately
Italy	Cascinelli et al[33]	1994–2005	Two-center prospective	Prognostic significance of SN biopsy, and status of nonsentinel nodes	1,108 patients (stage IB/II)	Stage I–II: 90.6% Stage III: 75.4% (81.4% one positive lymph node, 39.6% two positive lymph nodes) (OS)	N/R
Italy	Mandala et al[34]	1998–2008	Single-center prospective	Clinical and histopathological risk factors that predict SN positivity and survival	1,251 patients (stage I/II)	Stage I–II: 88.7% Stage III: 42.9% (OS)	Stage I–II: 75.9% Stage III: 35.2%
Italy	Testori et al[35]	2000–2002	Prospective from 23 centers. Median follow-up 4.52 years	Predictive factors of SN status and patients' prognosis after SN biopsy	1,304 patients (stage I–III)	Stage I–II: 91% Stage III: 67.7% (OS)	N/R
Italy	Quaglino et al[36]	1980–2007	Single-center prospective. Median follow-up 18.4 years	Clinical features of melanoma-associated vitiligo, association with other autoimmune manifestations and their effect on prognosis	2,954 patients (stage I–IV) of which 83 have vitiligo	Stage I: 95.4% Stage II: 68.8% Stage III: 42.5% Stage IV: 9.6 months median survival (OS for patients without vitiligo)	Stage III: 21.5%
Italy	Mandalà et al[37]	1998–2009	Single-center prospective. Median follow-up 3.5 years	Association of SES with Breslow thickness and survival	1,443 patients (stage I/II)	Stage I/II: 91.6%–98.3%: range by low to high SES (10-year OS)	Stage I/II: 81.7%–91.8%: range by low to high SES (10-year RFS)
Poland	Nowecki et al[38]	1997–2004	Single-center prospective. Median follow-up 3 years	Survival analysis and clinicopathological factors associated with false-negative SN biopsy	1,207 patients (stage I–III)	Stage I–II: 87.9% Stage III: complete lymph node dissection: 56.8% (OS) Stage III (false negative): 53.7%	N/R

Poland	Rutkowski et al[39]	1994–2007	Three-center prospective. Median follow-up 49 months	Outcomes of patients with clinical nodal melanoma metastases (known primary tumor – MKP – compared to unknown primary – MUP)	459 patients (stage IIIB/C)	Stage IIIB/C: MKP 36.0% MUP 41.4% (OS)	Stage III B/C: MKP 28% MUP 44%
The Netherlands	de Vries et al[40]	1995–2009	Single-center prospective. Median follow-up 64.8 months	Long-term outcome after SN biopsy	429 patients (stage IB–II)	5-year OS: Stage I–II: 80.3% Stage III: 67.1% 10-year OS: Stage I–II: 70.1% Stage III: 54.5% 10-year DSS: Stage I–II: 77.0% Stage III: 59.9%	Stage I–II: 71% Stage III: 48% (10-year RFS)
UK	Kettlewell et al[41]	1996–2003	Single-center prospective. Mean follow-up 42 months	Study to establish the prognostic value of knowledge of SN status in melanoma	472 patients (stage IB–III)	Stage I–II: 80%[a] approximately Stage III: 35%[a] approximately (OS)	Stage I–II: 82% Stage III: 42%

Notes: Survival reported is at 5 years from Kaplan–Meier analysis unless otherwise specified: OS or DSS. [a]Data were extracted from figures.
Abbreviations: OS, overall survival; DSS, disease-specific survival; RFS, recurrence-free survival; SN, sentinel node; SES, socioeconomic status; N/R, not reported.

Ten studies were designed to study outcomes after SN biopsy in early-stage CMM, with follow-up to more advanced disease.[28–30,32–35,38,40,41] These studies do not report stage, rather they report the outcome of SN biopsy (negative or positive). It is possible to assume that a patient with a negative SN biopsy is stage I or II, while those with a positive SN are stage III (or possibly stage IV) CMM. Survival in SN-negative patients is consistently higher than that for SN-positive patients: range 80%–95% at 5 years compared to 35%–75%, respectively. Recurrence-free survival rate at 5 years ranges from 76% to 90% in SN-negative patients and from 35% to 58% in SN-positive patients. Of the remaining four observational studies listed in Table 4, one study was designed to look at recurrence and survival in a large registry study,[31] one studied CMM associated vitiligo,[36] one studied the effect of socioeconomic status (SES) on survival,[37] and the final study[39] reported the outcomes in patients with unknown primary disease compared to those with known primary disease.

Discussion

To our knowledge, this is the first systematic review of stage-specific survival and recurrence of CMM patients in Europe. Our review identified a relatively small number of published studies (n=26) with over 400 patients and stage-specific outcome data. These were predominantly based in Northern Europe, where considerably higher CMM incidence rates are reported,[44] compared with southern Europe, and survival is known to be better.[6] Apart from the differences in the incidence and survival between countries, there are also differences in screening, early detection, treatment, and follow-up. Straightforward between-country comparisons are complicated by the large differences observed in study design and patient inclusion criteria, treatments, patient numbers, measurements reported for survival and recurrence, and duration of follow-up. The data provided by the identified studies, when taken collectively, provide an informative general overview of the range and variability of CMM stage-specific treatment outcomes in Europe, as well as of the research gaps, which are evident in this area. Patients included in these studies were diagnosed between 1978 and 2011. The SN biopsy procedure, introduced in the 1990s, has likely led to stage migration in all European countries where it has been implemented. This may mean that some patients previously classified as stage I and II are now being categorized as stage III. This may have led to a perceived improvement in survival for stages I and II, because patients with microscopically positive lymph nodes

and poorer prognosis are now correctly being classified as stage III. At the same time, the stage III group may now include patients with a relatively better prognosis (with microscopically positive lymph nodes), which may have led to an overall improved prognosis in stage III CMM (so-called Will Rogers phenomenon).[16]

Currently, 5-year relative survival after CMM in Europe is, overall, 83%, with variation by country and region.[6,9] Survival after a diagnosis of CMM varies widely by stage, and, in this review, we confirmed a large variability in survival. We included five large population-based registry studies from Denmark, Germany, Sweden, and the Netherlands: survival reported varied by study.[18–20,42,43] The German,[18] the Danish,[43] and one of the Swedish studies[42] reported relative survival; the Dutch study[20] reported the crude all-cause survival; and the other Swedish study[19] reported the crude disease-specific survival (DSS). Five-year survival in stage IV disease was the lowest in the Dutch study and was better in the Swedish (18%) and German studies (18%–28%). The completeness of stage at primary diagnosis and mortality data in all five registries is thought to be comprehensive; however, it is not known how accurately recurrence is reported. The Swedish study[19] linked several population-based nationwide registers and censuses, including the Swedish Melanoma Register and the Swedish Cancer Registry, for which completeness of information at diagnosis is known to be very high. In the Dutch national cancer registry, all newly diagnosed malignancies are recorded, and it has nationwide coverage since 1989, whereas the Danish cancer registry began systematic data collection in 1943, and registration has been mandated by administrative order since 1987.[45]

The reported stage-specific information, for both survival and recurrence, varies widely in the other non-population-based studies included in our review (both RCTs and observational studies). Specific studies, which reported survival and recurrence by different sociodemographic, biological, and clinical patient backgrounds identified that survival rates may be substantially affected by these factors. For example, substantial differences in survival are reported by SES. Stage I/II OS ranged from 91.6% for low SES patients to 97.3%–98.3% for middle/high SES patients.[37] This is mostly likely due to differences in early detection, as well as treatment patterns and follow-up.[19] Three studies included OS and DSS estimates according to number of lymph nodes involved in CMM patients, with all studies reporting substantial differences.[20,32,33] For example, the Dutch registry study and an Italian retrospective study reported approximately half the 5-year OS rate when two or more lymph nodes were involved compared to only one lymph node involved (27.1% versus 50.1% for the Dutch study; 39.6% versus 81.4% for the Italian study).[20,33] This further supports the importance of adequate substaging of stage III CMM patients according to number of involved lymph nodes. Differences were also observed for RFS, for example, by SES (from 81.7% for low SES patients to 91.8% for high SES patients).[37]

Stage-specific recurrence-free survival rates were not reported from any of the large registry studies, probably due to a lack of structured follow-up reporting in these settings; consequently, the best sources for the assessment of recurrence risk by stage were RCTs (Table 3), while nine observational studies also reported recurrence-free survival rates (Table 4). As was the case with the reported stage-specific survival data, most of the studies reporting recurrence outcomes had defined inclusion criteria in terms of the CMM stage their patient population sample comprised.

Limitations

Although the five registry studies[18–20,42,43] included are assumed to be of higher quality than the small-sized single-center studies, in practice, most registries may suffer from various degrees of underreporting. While the Swedish, the Danish, and the Dutch registry studies are nationwide population studies with high coverage of the national population, the German study covered only a section, 40%, of the population. This could mean that regional differences in CMM prevalence and quality of diagnosis and treatment options can influence stage at diagnosis and related survival. Also, the lack of completeness in stage-specific information at recurrence in the registry studies as well as incomplete information on histopathological prognostic factors may influence the reported results. For example, more than 5,000 patients in the Swedish study had unknown stage of disease at diagnosis.

Furthermore, registry studies may not capture follow-up data as accurately as prospective cohort studies or RCTs. Missing information on death, owing to incompleteness of follow-up, may have a disproportionate effect on survival estimates, although linking of registries to national cause of death registries limits this bias.[19,20] In addition, changes in treatment strategies like sentinel lymph node biopsy and staging classification provides further challenges for the interpretation of the overall data.

The data generated from seven RCTs included in our study may not be representative of survival patterns in the general patient population, because the trial populations are typically highly selective due to strict inclusion and exclusion criteria; however, they also provide data with high quality

since the follow-up may have been more stringent. Indeed, it may be valuable for potential authors interested in performing a trial with similar inclusion criteria to have the available data from these RCTs listed in our review.

Most of the identified studies had defined inclusion criteria in terms of CMM stage and treatments under review. In effect, this limited the reporting of stage-specific data to subsets of patients for each study. However, when taken together, the studies cover all CMM stages and, hence, provide an overview of the general landscape in Europe in terms of stage-specific survival.

It should also be emphasized that it is challenging to compare data from different timeframes owing to the change in behavior (sun exposure) and awareness over time. Interventions such as SN procedures have also resulted in a change in staging, with more accurate staging in recent years.

Conclusion

The studies identified in this review highlight large variations in stage-specific survival and rates of recurrence between European countries. From the 26 included studies, which represented nine countries, stage-specific information for survival and recurrence varied: 5-year OS rates were 95%–101% (stage I), 65%–92.8% (stage II), 41%–71% (stage III), and 9%–28% (stage IV); 5-year RFS was reported less frequently: 56% (stage II) and 28%–44% (stage III).

Owing to differing study designs and populations, it is difficult to make detailed comparisons between studies. It is likely that differences in country guidelines and success in early diagnosis of CMM, as well as approaches to treatment contribute to differences in reported outcomes. However, a number of studies included evaluations enabling comparisons in OS and recurrence-free survival estimates by key patient sociodemographic characteristics, which suggest that differences in these factors can result in substantial attenuation or reduction of the survival estimates for separate patient groups. Further large-sample population-based studies are needed to provide a more comprehensive overview of patterns of CMM stage-specific survival within European populations.

Changes in epidemiology may be of relevance for planned future studies in CMM, with new agents likely to enter the adjuvant setting. Recently in Europe, stage migration toward less-advanced CMM at diagnosis and a shift in distribution toward higher proportion of patients with better prognosis have been seen. This can lead to underestimation of required sample size and a delay until clinical trials report outcome. In addition, the degree of heterogeneity in treatment of early-stage CMM in different parts of Europe and its impact on clinical outcome is not well characterized. A characterization of stage-specific risk of recurrence and survival in more modern cohorts is thus relevant from a clinical and patient perspective and might also be helpful in the design of clinical trials.

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Supplementary materials

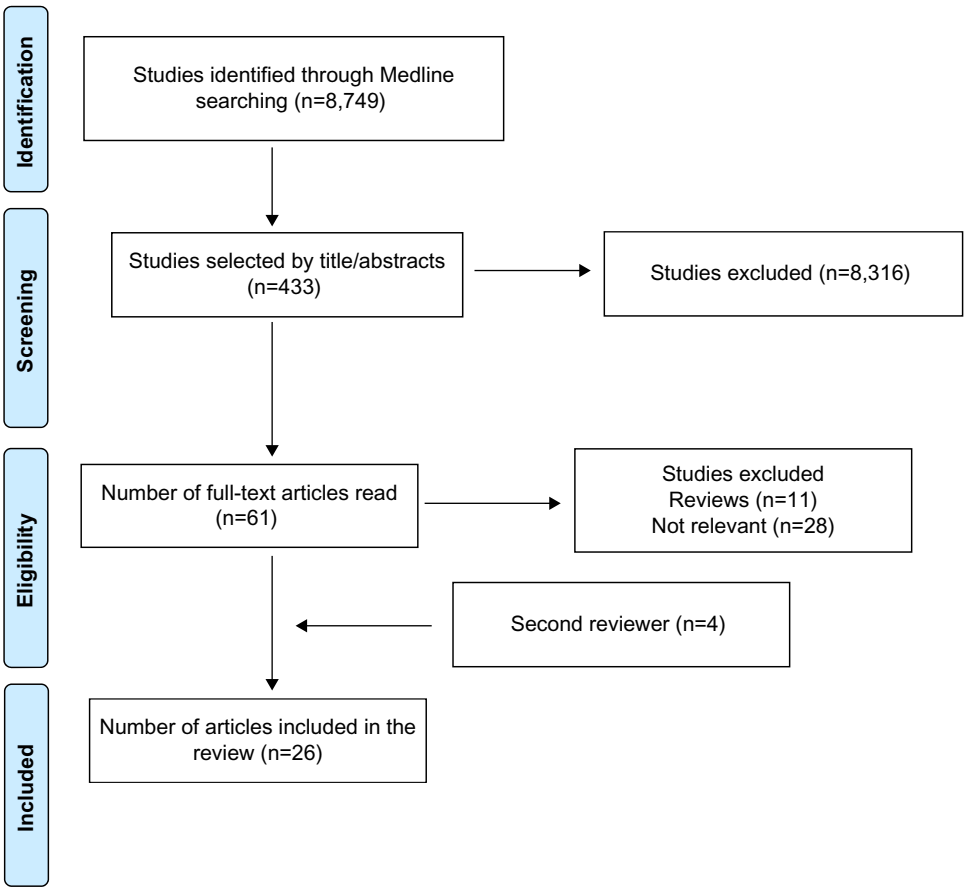

Figure S1 Search flow diagram (according to the PRISMA statement).
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table S1 PRISMA systematic review reporting checklist

Section/topic	#	Checklist item	Reported at
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	Methods
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, and publication status) used as criteria for eligibility, giving rationale.	Methods
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, Supplementary material
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	Methods, Supplementary material
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	Methods, Discussion
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	N/A
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Supplementary material
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Tables 1–4

(*Continued*)

Table S1 (*Continued*)

Section/topic	#	Checklist item	Reported at
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12)	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group and 2) effect estimates and confidence intervals, ideally with a forest plot.	Tables 2–4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	Acknowledgment of Research Support/Disclosures/Conflicts of Interests

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; N/A, not applicable.

Table S2 Medline search command

Key concept/s	Term
Melanoma	("Melanoma" [Mesh] OR "malignant melanoma" [all fields])
	AND
Survival	("Survival" [Mesh] OR "Mortality" [Mesh] OR "Death" [Mesh] OR "Disease Progression" [Mesh]
Recurrence	OR "Recurrence" [Mesh] OR "Neoplasm Metastasis" [Mesh] OR "metasta*" [all fields] OR "General
Additional relevant keywords	Surgery" [Mesh] OR "surgery" [all fields] OR "surgical" [all fields] OR "resection" [all fields])
	NOT
Geographical restriction	("America" [all fields] OR "American" [all fields] OR "Australia" [all fields] OR "Australian" [all fields] OR "Canada" [all fields] OR "Canadian" [all fields] OR "Japan" [all fields] OR "Japanese" [all fields] OR "Brazil" [all fields] OR "Brazilian" [all fields] OR "China" [all fields] OR "Chinese" [all fields] OR "India" [all fields] OR "New Zealand" [all Fields] OR "Africa" [all fields] OR "African" [all fields] OR "Korea" [all Fields] OR "Korean" [all fields] OR "Mexico" [all fields] OR "Mexican" [all fields])
	AND
Publication date	("2004/01/01" [PDAT]: "2015/12/31" [PDAT])
	AND
Language restriction	English [lang]

Notes: Date last search was performed: January 26, 2016.