Review

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Melanoma Management

Epidemiology and survival outcomes in stages II and III cutaneous melanoma: a systematic review

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Practice points

- There are limited publications on the epidemiology of stages II and III cutaneous melanoma (CM) specifically.
- Incidence rates for stages II and III CM were only reported for US and Swedish populations.
- None of the studies identified in this review reported specific prevalence data for stages II and III CM.
- Survival rates were reported in 33 publications across four continents but heterogeneity in study characteristics makes comparison challenging.
- Five-year disease-specific survival rates ranged from 63–81% in stage II CM, with most studies reporting a rate of over 70%.
- Five-year disease-specific survival rates ranged from 36–63% in stage III CM, with most studies reporting a rate of over 50%.
- We have been unable to gain conclusive knowledge of epidemiology in stages II and III CM.
- Our review highlights that further epidemiological studies focused in stage II and/or III CM are needed to inform and target treatment for better management of the disease.

Aim: Management of cutaneous melanoma (CM) is continually evolving with adjuvant treatment of earlier stage disease. The aim of this review was to identify published epidemiological data for stages II–III CM. **Materials & methods:** Systematic searches of Medline and Embase were conducted to identify literature reporting country/region-specific incidence, prevalence, survival or mortality outcomes in stage II and/or III CM. Screening was carried out by two independent reviewers. **Results & conclusion:** Of 41 publications, 14 described incidence outcomes (incidence rates per stage were only reported for US and Swedish studies), 33 reported survival or mortality outcomes and none reported prevalence data. This review summarizes relevant data from published literature and highlights an overall paucity of epidemiological data in stages II and III CM.

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Cutaneous melanoma (CM), a malignant neoplasm that develops from melanocytes, is the most commonly occurring form of melanoma [1]. Over the last 3 decades, the global incidence of CM has steadily increased and the International Agency for Research on Cancer has predicted that this pattern will continue [2]. In 2018, the estimated age-standardized global incidence rate for CM was 3.1 per 100,000 persons, with nearly 300,000 new cases diagnosed and 60,000 deaths reported for the same year [3]. There has been an emphasis on early detection and the need for better therapeutic strategies at an earlier stage of disease, as advanced disease predicts poorer patient outcomes [4]. Treatment pathways for CM are continuously evolving. For patients with clinical stage II (dermal spread of the tumor) or III melanoma (regional lymph node spread), surgical excision is the standard approach; however, subsequent relapse is experienced by some individuals. Advances in the use of immunomodulating agents

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and targeted therapies for treating metastatic disease has led to the assessment and use of such drugs in the adjuvant setting for stage III patients at high risk of recurrence following surgery [5]. The efficacy of such therapies is yet to be established in stage II patients; however, clinical trial data may guide their use in practice [6]. With these factors considered, analysis of the global epidemiology for clinical stages II and III CM populations is necessary to better inform disease burden and treatment protocols.

We conducted a systematic literature review with the objective of gaining insight into global epidemiological data for the stage II and/or III CM population. We analyzed published literature reporting country- or region-specific incidence, prevalence, survival and mortality outcomes. To our knowledge, no published systematic reviews of the global epidemiology and survival/mortality rates of stages II and III CM are available.

Materials & methods

The methodology for conducting this systematic literature review was documented in a review protocol. The process was conducted in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses statement [7].

Search strategy

Systematic searches of Medline and Embase were conducted up to 28 January 2019, to identify studies reporting outcomes for incidence, prevalence, survival and mortality in stage II and/or stage III CM populations. There were no restrictions on language, country, publication type and timeframe to initially keep the scope broad. A range of search terms related to incidence, prevalence, survival and mortality (e.g., death, fatal) and stage II and III disease (e.g., 'stage 3' or 'stage III' or 'stage three' or 'stage 3a' or 'stage IIIa' or 'stage three a' or 'stage 3b' or 'stage IIIb') were used (Supplementary Figure 1). Hand-searching was performed to supplement the electronic searches. This included cross-referencing relevant systematic reviews and reference lists of included peer-reviewed publications and free text keyword searching in internet search engines.

Eligibility criteria

Two reviewers independently screened titles and abstracts to determine eligibility for inclusion in this review. Any discrepancies were resolved by discussion, with a third reviewer assessing sources for which a decision could not be reached. Full-text English language publications were retrieved and assessed by the same method. All publications were screened against prespecified criteria, with studies reporting incidence or prevalence in stage II and/or III CM from a regional or national general population, included for review. Publications reporting incidence data that identified patients from a national database or registry were also included. Incidence rates and incident cases (where incidence rates were unavailable) were captured. An incidence rate is defined as the number of new cases divided by the number at risk in a specified population within a given period and is typically reported as cases per 100,000 persons per year [2]. An incident case describes a newly diagnosed individual at particular timepoint [8]. Studies that included patients with mucosal and uveal melanomas, subungual melanoma or melanoma of unknown primary region were excluded. Population sizes associated with survival or mortality outcomes were not considered a limiting factor for study inclusion. In order to summarize the most up-to-date published epidemiological data on CM, publications from the last 10 years only (2009 onward) were included.

Quality assessment

Methodological quality assessment of the included literature was conducted using two separate tools. The Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies was used to assess bias in included studies which reported incidence and prevalence [9]. The Risk of Bias Assessment Tool for Non-randomized Studies was adapted to assess included observational studies reporting survival and mortality outcomes [10].

Results

The electronic search strategy identified 2835 publications. Three additional publications were identified from hand-searching. Following the removal of duplicate records, 1942 publications were assessed for eligibility. A total of 91 publications were eligible for inclusion based on title/abstract screening. In total, 41 publications were included either as full-text peer-reviewed publications (n = 35) or as conference abstracts (n = 6). A total of 14 publications reported incidence data and none reported prevalence data. A total of 33 reported survival and mortality rates in the stages II and/or III melanoma populations (Supplementary Figure 2).

Table 1. Publications reporting incidence rates in stage II and/or III cutaneous melanoma.

Study (year)	Geographical location	Total population size estimate (reported in the publication)	Data source	AJCC staging criteria	Stage of disease	Study timeframe	Timeframe breakdown	Incidence rate (per 100,000 persons/year)	Ref.
USA									
Fleming (2018)	USA (all 611 counties)	–	SEER† and AHRF	6th edition	Stage II	2008–2012	–	2.36 (SD: 2.07)	[11]
					Stage III		–	1.22 (SD: 1.22)	
	USA (138 counties with HPSA)	–			Stage II	2008–2012	–	2.07 (SD: 2.14)	
					Stage III		–	1.25 (SD: 1.64)	
Tarhini (2019)	USA	–	SEER†	7th edition	Stage III	2010–2014	2010	1.21	[12]
							2014	1.48	
				8th edition			2010	1.23	
							2014	1.47	
Europe									
Stromberg (2016)	Western Swedish healthcare region, Sweden	1,490,000 (adult population in 2013)	Population-based national cancer register, linked to additional data from the National Swedish Melanoma Quality Register and Statistics Sweden register	6th edition	Stage II	2004–2013	–	5.0‡ (95% CI: 4.7–5.3)	[13]
	Southern Swedish healthcare region, Sweden	1,450,000 (adult population in 2013)					–	3.6‡ (95% CI: 3.4–3.8)	

See Supplementary Table 1 for breakdown of incidence rates per year in stage III cutaneous melanoma according to the 7th and 8th AJCC editions.
†SEER database represents approximately 30% of the US population [14].
‡Reported as age-adjusted incidence rate (per 100,000 persons per year).
AHRF: Area Health Resources files; AJCC: American Joint Committee on Cancer; HPSA: Health professional shortage area; NR: Not reported; SD: Standard deviation SEER: Surveillance, Epidemiology and End Results program.

A total of 20 publications were excluded at full-text due to lack of relevant data; most of these publications reported outcomes combined across multiple disease stages (e.g., including stage I and/or IV) and therefore data specific to stage II and/or III could not be separately extracted. In addition, 20 publications were excluded because they reported data for a melanoma population that was not of interest for this review (e.g. patients with uveal melanoma). Seven publications were excluded for reporting duplicate data and three were not published in the English language (Supplementary Figure 2).

A narrative approach has been taken for this review due to differential reporting of incidence and survival data between studies.

Characteristics of included incidence studies

Outcomes from included incidence studies were captured and reported in two separate data tables: publications reporting incidence rates (Table 1) and publications reporting country- or region-specific incident cases (Table 2).

A single Swedish study reported age-adjusted incidence rates for the stage II melanoma population [13]. Unadjusted incidence rates for stages II and III melanoma populations were reported in two studies from the USA (Table 1) [11,12].

In the identified publications, data were mostly reported as the number of incident cases within a specific country/region over a specified timeframe (n = 14). Of these publications, five reported the size of the general population from which the incident cases were identified. For the remaining studies, we sourced country-specific population estimates using a recent United Nations report (Table 2) [26]. Three studies reported stage II/III data from the USA [12,24,25] and ten studies reported stage II and/or III in seven European countries covering Denmark [15], England [16], Estonia [18], Germany [23], the Netherlands [17], Sweden [13,19,21,22] and Spain [20].

Incidence rates in stages II & III melanoma

Overall, three studies reported incidence rates in stage II and/or III CM (Table 1). Stromberg *et al.* compared age-adjusted incidence rates between the Swedish western healthcare and Swedish southern healthcare regions from 2004 to 2013 in the stage II population, reporting a rate of 5.0 (95% CI: 4.7–5.3) and 3.6 (95% CI: 3.4–3.8) per

Table 2. Publications reporting incident cases in stage II and/or III cutaneous melanoma.

Study (year)	Geographical location	Total population size estimate	Data source	AJCC staging criteria	Stage of disease reported	Study timeframe	Timeframe break-down	Total number of incident cases	Ref.
Europe									
Bay (2014)	Denmark	2004: 5,403,000†	DCR	–	Stage II	2004–2011	–	1393	[15]
		2011: 5,583,000†	–		Stage III	–	–	850	
Herbert (2018)	East Anglia, England	2,500,000‡	Population-based cancer registry for the Anglia and successor organizations (Public Health England National Cancer Registration and Analysis Service)	4th edition	Stage II	1996–2015	1996–2000	349	[16]
							2001–2005	449	
							2006–2010	572	
							2011–2015	652	
Leeneman¶ (2018)	The Netherlands	1989: 14,869,000†	NCR	–	Stage II	1989–2016	–	11,402	[17]
		2016: 16,987,330†		–	Stage III	–	–	8,946	
Padrik (2017)	Estonia	1,340,000‡ (population in 2011)	ECR	7th edition	Stage II	1995–2012	1995–1999	254	[18]
							2000–2004	327	
							2005–2009	281	
							2010–2012	144#	
					Stage III		1995–1999	63	
							2000–2004	58	
							2005–2009	111	
							2010–2012	71#	
Plym (2014)	Uppsala/Örebro healthcare region, central Sweden	2,000,000‡	Quality Register of Cutaneous Malignant Melanoma (represents 21% of Sweden's population – estimated at 2,000,000 during study period)	6th edition	Stage II	1997–2011	–	1555	[19]
					Stage III			332	
Rios (2013)	Spain	1997: 40,131,560† 2011: 46,909,138†	RNMC (cases from across all 17 autonomous regions; no % population coverage reported)	7th edition	Stage II	1997–2011	–	378	[20]
					Stage III			231	
Rockberg (2016)	Stockholm, Sweden	2,123,337‡ (Stockholm county population in 2012)	Hospital records and data from five national databases	7th edition	Stage II	2005–2012	2005	78	
							2006	81	
							2007	79	
							2008	91	
							2010	110	
							2011	122	
							2012	107	
					Stage III		2005	20	
							2006	40	
							2007	51	
							2008	33	
							2009	24	
							2010	29	
							2011	19	
							2012	23	
Simberg–Danell (2016)	Sweden	1990: 8,576,000†	SMR (population coverage ~95%)	6th edition	Stage II	1990–2007	–	5757	[22]
		2007: 9,163,000†			Stage III	–	–	609	
Schoffer (2016)	Germany	2002: 81,535,000	Population-based (n = 24) and hospital-based (n = 4) cancer registries	UICC§	Stage II	2002–2011	2002	814	[23]
							2003	642	
							2004	742	
							2005	745	
							2006	738	
							2007	744	
							2008	761	
							2009	734	
							2010	712	
							2011	720	
		2011: 80,856,000			Stage III		2002	260	
							2003	296	
							2004	327	
							2005	355	
							2006	360	
							2007	390	

100,000 persons/year, respectively (Table 1). The age-adjusted incidence rate was combined for stages III and IV so this data cannot be reported in this review. However, notably, disease mapping within the study showed a higher frequency of earlier stage tumors (stages I–II) in the western region and conversely, more advanced stage tumors (stages III–IV) in the southern region [13].

An incidence rate of 2.36 (SD: = 2.07, 0–19.4) per 100,000 persons/year for stage II patients between 2008 and 2012 was reported by Fleming *et al.* in a population-based US study (Table 1) [11]. The study explored the association between the density of primary care providers (PCPs) and melanoma incidence, using population data from the Surveillance, Epidemiology and End Results program (SEER) which represents approximately 30% of the US population [14]. Notably, in the counties designated Health professional shortage areas (n = 138), an incidence rate for stage II disease of 2.07 (SD: = 2.14, 0–12.9) per 100,000 persons/year was reported for the same period (Table 1). The results showed a statistically significant correlation between a higher PCP density and overall higher melanoma diagnosis rate for this stage of disease [11]. When studying the same outcome in stage III disease, there was no statistically significant association between incidence and PCP density. For stage III disease, a rate of 1.22 per 100,000 persons/year (SD: = 1.22, 0–8.95) was reported, compared with 1.25 (SD: = 1.64, 0–8.95) per 100,000 persons/year in health professional shortage areas (Table 1) [11]. Another US study which assessed incidence rates in the SEER program, showed an increase in the stage III incidence rate between 2010 and 2014 from 1.21 to 1.48 per 100,000 persons/year (based on American Joint Committee on Cancer [AJCC] 7th edition staging criteria; Table 1). Similar rates were observed when AJCC 8th edition staging criteria was used (2010, n = 1.23 per 100,000 persons/year; 2014, n = 1.47 per 100,000 persons/year) [12]. The statistical significance of this increase was not reported. Despite a small difference between incidence rates, AJCC edition had little observable effect on the incidence of stage III overall; however, at a substage level, the effect of AJCC staging criteria was more apparent. For example, the incidence (per 100,000 persons/year) of stage IIIc in 2010 was higher based on AJCC 8th edition (0.42; 95% CI: 0.38–0.46) compared with AJCC 7th edition (0.27; 95% CI: 0.24–0.3). Based on AJCC 7th edition, incidence of stage IIIc increased from 0.27 (95% CI: 0.24–0.3) to 0.34 (95% CI: 0.31–0.37) per 100,000 persons/year from 2010 to 2014. When applying AJCC 8th edition criteria, this led to a greater increase over the same time period, from 0.42 (95% CI: 0.38–0.46) to 0.54 (95% CI: 0.5–0.59) per 100,000 persons/year (Supplementary Table 1).

Incident cases in stages II & III melanoma

Incident cases in stage II melanoma

Stage II incident cases were reported in 13 publications. We identified data from three US studies [12,24,25] and ten European studies (Table 2) [13,15–21,23]. The number of incident cases were reported for a range of timeframes covering the period from 1989 to 2016, using data identified from national cancer registries and hospital records. Publications did not consistently report the size of the general population at the time of data collection, limiting interpretation of the number of incident cases. Additionally, the data source used did not always represent the total melanoma population within the region or country. For example, two studies reported a disparate number of incident cases for a US population; Bhatt *et al.* reported 59,424 stage II cases over a 12-year period from the National Cancer Database database [24] and Evans *et al.* reported 9985 cases over a 5-year period from the SEER program database. This difference is likely driven by the higher coverage of National Cancer Database (70%) than [27] that of SEER (30%) [14].

A number of retrospective studies analyzed the number of stage II incident cases over a series of discrete time periods (typically every year or every 5 years) [13,16,18,21,23]. Of these, three reported an increase in stage II incident cases over time [13,16,21]. These increases occurred in the southern and western healthcare regions of Sweden (2004–2008, n = 1,117; 2009–2013, n = 1,253) [13], East Anglia in England (1996–2000, n = 349; 2001–2005, n = 449; 2006–2010, n = 572; 2011–2015, n = 652) [16] and in Stockholm (2005–2008, n = 329; 2009–2012, n = 417) [21]. Herbert *et al.* also conducted an analysis of stage-specific trends in melanoma incident cases in East Anglia (England) from 1996 to 2015 (Table 2). Adjusted incidence rate ratios indicated statistically significant increases for all melanoma stages [16]. In particular, they observed a 3% increase per year (95% CI: 2–4%) for stage II melanoma [16]. One study in Germany reported an overall decline in the number of cases (2002, n = 814; 2011, n = 720); however, the number of cases remained relatively constant from 2003 onward [23].

Incident cases in stage III melanoma

Stage III incident cases were reported in 12 publications. We identified data from three US studies [12,24,25] and nine European studies (Table 2) [13,15–23]. The number of new cases was generally reported for the whole study timeframe, meaning analysis of trends over time was not feasible.

Fluctuations in incident cases over time in stage III CM were reported by four publications covering Estonia, Germany and Sweden [13,18,21,23]. Incident cases in Estonia from 1995 to 2012 were reported by Padrik *et al.* from the Estonian Cancer Registry. Data over the 18-year period were presented in three 5-year periods (1995–1999; 2000–2004; 2005–2009) and one 3-year period (2010–2012; Table 2). The number of incident cases peaked between 2005 and 2009 (n = 111); however, as the final timeframe was only 3 years (2010–2012; n = 71), it is not possible to determine a trend [18]. Data from the southern and western healthcare regions of Sweden showed a clear increase in the number of stage III cases. Significantly, cases nearly doubled over two specified time periods (2004–2008, n = 173; 2009–2013; n = 330; Table 2). In the Stockholm region, the highest number of incident cases were reported in 2007 (n = 51) before a gradual decline was observed [13]. Data for a German population also showed an overall increase in the number of cases (2002, n = 260; 2011, n = 392; Table 2) [23].

Two publications reported incident cases in stage III CM in the USA from the SEER database between 2010 and 2014 [12,25]. Evans *et al.* reported 4953 new cases of stage III disease over the 5-year period [25], compared with Tarhini *et al.* who reported 7669 (Table 2) [12]. Although both studies used the SEER database, each identified a different number of melanoma patients; Evans *et al.* identified 103,777 patients using CS Schema v0204+ before applying exclusion criteria [25], while Tarhini *et al.* identified 191,232 patients and did not stipulate the method used [12]. Despite the difference in the number of incident cases reported in studies, a percentage analysis demonstrated that stage III patients comprised around 7% of all melanoma patients in each study [12,25].

Survival outcomes in stages II & III melanoma

A summary of publications reporting survival and mortality rates in stage II and/or III melanoma is presented in Table 3. Variables including cohort size, survival definition, treatment or diagnosis period and interventions given to patients make data interpretation challenging and prohibit direct comparisons. For the purpose of presenting a clear dataset, weighted means have been calculated for publications with complex subgroup data (Table 3). Subgroup breakdown is provided in Supplementary Tables 3–8.

Five-year disease-specific survival rates in stage II melanoma

Disease-specific survival (DSS) is defined as the percentage of people in a study or treatment group who have not died from a specific disease in a defined period of time [55]. The term melanoma-specific survival (MSS) is also supported by this definition and was used in several publications. A total of four studies from the USA or Japan reported either DSS or MSS rates in a stage II melanoma population (Table 3) [25,34,36,51]. A 5-year MSS rate of 81% was observed among a cohort of 738 patients treated between 1993 and 2013 in the USA [34]. Another US study by Evans *et al.* reported a 5-year DSS rate of 78% for 9985 stage II patients diagnosed between 2010 and 2014 [25]. A Japanese study comparing survival between patients who received adjuvant DAV-IFN-β therapy and those who did not between 1998 and 2009, reported 5-year MSS rates of 88 and 76%, respectively (Table 3) [51]. A propensity score-matched analysis used to adjust for confounding revealed no significant difference between the two study arms [51]. Overall, 5-year DSS and MSS rates in stage II ranged from 63–81% with most studies reporting a rate of over 70% (Table 3).

Five-year DSS rates in stage III melanoma

Ten studies reported 5-year DSS or MSS rates in a stage III population; four in the USA, four in Europe, one in Asia and one in Australia (Table 3) [25,28,32,37,40,43,44,46,51,53]. Single-center data reported by Bowles *et al.* showed a 5-year 52% traditional DSS rate in 760 patients treated between 1990 and 2001 in the USA (Table 3) [32]. Notably, stage IIIb and IIIc patients made up 82% of the stage III population. Further, substage analysis showed that stage IIIa patients had a higher 5-year DSS rate of 78% [32]. This study also reported conditional survival estimates, noting that the 5-year conditional DSS for all stage III patients increased from 45% at time of diagnosis, to 89% for survivors at 5 years. The largest increase in conditional DSS from time of treatment to 5-year survival, was in stage IIIc (39–78%) [32]. Martinez *et al.*, examined a substantially larger cohort from SEER (n = 6868) and observed a 5-year MSS rate of 59% for patients diagnosed between 1988 and 2006 (Table 3) [37]. When stratified by time period of diagnosis, the 5-year MSS rate was 51% for those diagnosed between 1988 and 1999 and 62% for those

Table 3. Publications reporting survival data in stage II and/or stage III cutaneous melanoma.

Study (year)	Geographical location for target population	Data source	Period of diagnosis or treatment of cohort	Stage of disease	Size of cohort	Definition of survival rate	Time period	Mean survival rate (%)	Recurrence-free DFS (%)	Ref.
USA										
Balch (2010)	USA	AJCC melanoma-staging database	–	Stage III	2313	OS	5–year	63	–	[28]
Balch‡ (2011)	USA	AJCC melanoma-staging database	–	Stage III	634	–	5-year	61	–	[29]
							10-year	45		
Balch (2013)	USA	AJCC melanoma-staging database	–	Stage III	2267	MSS	5-year	63§	–	[30]
Balch (2014)	USA	AJCC melanoma-staging database	–	Stage II	–	–	–	–	–	[31]
Bowles (2010)	USA	University of Texas MD Anderson Cancer Center	1990–2001 (patients treated)	Stage III	760	DSS	5-year	52	–	[32]
							10-year	43		
						DFS	5-year	38	–	
							10-year	31		
Dawes (2016)	USA	SEER	1992–2009 (diagnosis period)	Stage II	12,635	OS	5-year	66§	–	[33]
				Stage III	6568			58§		
Lee (2017)	USA	MSKCC database	1993–2013 (patients treated)	Stage II	738	MSS	5-year	81	–	[34]
Evans (2018)	USA	SEER	2010–2014 (diagnosis period)	Stage II	9985	DSS	5-year	78	–	[25]
				Stage III	4953				60	
Kurtz (2017)	USA	James Cancer Registry	2009–2015 (patients treated)	Stage II	146	RFS	5-year	–	87	[35]
				Stage III	101				77	
Lowe (2014)	USA	REP	1970–2009 (diagnosis period)	Stage II	16	DSS	5-year	63§	–	[36]
Martinez (2011)	USA	SEER	1988–2006 (diagnosis period)	Stage III	6868	OS	5-year	51	–	[37]
						MSS		59		
Song (2015)	USA	SEER	2004–2009 (diagnosis period)	Stage IIIb/c	74	–	1-year	67	–	[38]
							2-year	43		
							3-year	32		
Tan (2019)	USA	BIDMC Cutaneous Oncology Program	1995–2011 (patients evaluated)	Stage II	45	OS	5-year	57		[39]
				Stage III (IIIa)	83			78		
Europe										
Bay (2014)	Denmark	Danish Cancer Registry	2004–2008 (diagnosis period)	Stage II	771	RS	5-year	83	–	[15]
				Stage III	516			65		
Plym (2014)	Sweden	Regional Quality Register of Cutaneous Malignant Melanoma	1997–2011 (diagnosis period)	Stage II	1555	RS	5-year	72	–	[19]
				Stage III	322			49		
Rockberg (2016)	Sweden	Hospital records and data from five national databases	2005–2012 (diagnosis period)	Stage II	746	OS	5-year	62	60	[21]
						RFS				
				Stage III	239	OS		57	17	
						RFS				
Elsaesser (2012)	Germany	Department of Dermatology, University Tübingen records	1996–2009 (diagnosis period)	Stage II	781	OS	5–year	82	–	[41]
				Stage III	214			69		
Heisen‡ (2014)	The Netherlands	NCR	2003–2011 (diagnosis period)	Stage IIIc	414	–	1-year	71	–	[42]
							2-year	48		
							3-year	33		
							5-year	25		
							9.6-year	21		
Madu (2016)	The Netherlands	Netherlands Cancer Institute–Antoni van Leeuwenhoek	2000–2015 (patients treated)	Stage IIIb		MSS	5-year	59	–	[43]
							10-year	52	–	
						DFS	5-year	–	47	
							10-year	–	41	
Niebling (2013)	The Netherlands	Hospital medical records, five centers	2003–2007 (referral period)	Stage IIIb/c	173	MSS	2-year	67	–	[44]
							5-year	48	–	
Leiter (2012)	Germany, Austria and Switzerland	German-based CMMR	1976–2007 (diagnosis period)	Stage II	7879	RFS	1-year	–	86	[45]
							3-year		72	
							5-year		66	
							10-year		57	

diagnosed between 2000 and 2006 (Supplementary Table 7) [37]. Based on univariate analysis, the treatment era was considered a statistically significant predictor of MSS ($p < 0.001$) [37].

A multicenter study reported a 5-year MSS rate of 48% in a cohort of stage IIIb and IIIc patients (n = 173) treated between 2003 and 2007 in The Netherlands (Table 3) [44]. Similarly, a single-center Dutch study, which assessed a larger patient cohort (n = 250) over a longer timeframe (2000–2015) reported a 5-year MSS rate of 59% in stage IIIb patients [43]. In a hospital-based Japanese study by Matsumoto *et al.*, an MSS rate of 65% was demonstrated in stage III patients treated with DAV-IFN-β therapy, compared to a rate of 36% in stage III patients not receiving DAV-IFN-β therapy [51].

Overall, DSS or MSS rates in stage III ranged from 36% to 63%, with most studies reporting a rate of over 50% (Table 3).

Five-year disease-free survival or recurrence-free survival rates in stage III melanoma

Disease-free survival or recurrence-free survival (RFS) is the length of time following a primary cancer treatment that a patient survives without any further signs or symptoms of that cancer [55]. Disease-free survival or RFS was reported in eight of the studies which met inclusion criteria for this review (Table 3) [21,32,35,43,45,49,51,53].

In a study of stage III patients treated between 2009 and 2015 in the USA, Kurtz *et al.* reported a 5-year RFS rate of 77% (Table 3) [35]. There was a statistically significant difference in 5-year RFS between disease stages. Notably, 5-year RFS rate in the stage IIc population was lower than that reported in the stage IIIa population; however, disease recurrence was experienced at an earlier timepoint for stage IIIa patients [35]. Comparatively, a 5-year RFS rate of just 17% was observed in a cohort of 239 patients in Sweden diagnosed between 2005 and 2012, despite a 5-year overall survival rate of 57% for the same patient group (Table 3) [21]. Data from Germany showed a 5-year RFS rate of 57% in a larger cohort of 1669 patients diagnosed between 1976 and 2007 [45]. The study also reported that as time progresses post-diagnosis, the risk of developing recurrence significantly decreases ($p < 0.05$) [45].

Quality assessment of epidemiology studies

Supplementary Figure 3 presents results from the Joanna Briggs Institute assessment. Strengths of the studies included their retrospective design, adequate sample size and the description of participant characteristics. Major limitations for many studies were the lack of clear population denominators, as this precluded calculation of incidence rates and cumulative incidence, in addition to lack of statistical analysis per melanoma stage. All studies employed a retrospective study design. Ten studies described valid methods to identify the condition, including the use of International Classification of Disease coding [11,12,16,18,19,21–25].

Domains from the Risk of Bias Assessment Tool for Non-randomized Studies were tailored to allow for consistent assessment across studies and results are presented in Supplementary Figure 4. A key strength of all the studies was appropriate selection and high inclusion of study participants in survival analyses. The major limitation was the lack of clear reporting on interventions given to patients, either in the form of surgical or adjuvant intervention [15,18,19,21,23,25,28–31,33,34,36–38,40–42,44,45,48–50,52–54].

Discussion

This review indicates a paucity of published incidence and prevalence data specific to stage II and III CM populations. Most of the included studies reporting incidence data are in US or Swedish population. Only three published studies provided incidence rates; Stromberg *et al.* presented an age-standardized incidence rate and the remaining two identified patients from the same data source (US SEER) [11–13]. There is a clear need for more epidemiological studies in this patient population. Despite the breadth of information that can be obtained from publicly available databases such as Globocan and IHME, these sources lack the granularity to obtain direct incidence/prevalence estimates by clinical stage.

Notably, our review yielded no published literature reporting incidence and prevalence of the stage II and III populations from Asian countries. This may in part be due to the rarity of the condition in this area of the world [56]. However, the review did capture mortality and survival data from four publications from China and Japan [49–52].

The apparent rise in incidence rates and incident cases of stages II and III CM reported by publications captured in this review could be suggestive of an overall increase in incidence in this patient population on a larger scale [12,13,16,18,21].

Most incidence data captured in this review were reported as incident cases. Unrepresentative population coverage of national databases combined with limited reporting of general population details in the included publications

restricts interpretation of trends in incidence. Crude incidence rates could be determined from incident cases using population sizes extracted from the UN database but would have to be interpreted with caution [26]. Further, change in general population size over time is a significant consideration for included studies, which reported general population estimates for a timepoint toward the end of their study period, as a crude incidence rate calculated from the reported data would likely underestimate incidence at the beginning of the study period [13,18,21]. Comparing adjusted incidence rates is preferred, to account for differences such as age and time of diagnosis within a population [57].

Incident cases reported in East Anglia (UK), Estonia, Germany and in different healthcare regions of Sweden could be used to estimate the change in the number of newly diagnosed cases over time and, in some cases, to identify specific timepoints of peak incidence. However, changes in general populations over time were not described for the included studies that reported absolute incident cases. Moreover, clinical stage was reported as unknown for some patients, meaning absolute numbers are difficult to compare within melanoma stage [15,18,22,24]. Consequently, we cannot accurately conclude any trends in incidence based on the results from this review.

Other literature suggests a higher rate of earlier stage diagnosis, which may be due to improved diagnosis, screening programs and public health awareness. In a study which assessed the correlation between the rate of skin biopsies and incidence of melanoma in the USA between 1986 and 2001, a mean biopsy rate increase of 2.5-fold among patients aged ≥65 was observed. During this period, incidence of melanoma increased from 45/100,000 persons to 108/100,000 persons, with 1000 additional biopsies, equating to an extra 6.9 melanoma diagnoses [58]. Notably, data reported by Padrik *et al.* showed a peak in the number of incident cases of stage II CM (n = 327) compared with the lowest number of incident cases of stage III (n = 58) during the same period in Estonia [18]. Moreover, data published by Fleming *et al.* showed a higher density of primary care providers was correlated with a higher number of stage II incident cases, suggesting patient access as well as public health awareness campaigns play a role in influencing higher incidence in earlier stage disease [11].

Stromberg *et al.* reported disparate age-adjusted incidence rates for stage II disease between the southern and western healthcare regions of Sweden [13]. This could be explained by several factors, including risk behavior and UV-exposure. These factors were also discussed by Padrik *et al.,* who referred to Estonia's increased accessibility and affordability of holidaying in sunny locations and use of tanning beds following an open market transition [18].

Changes to diagnosis or staging criteria over time may influence 'true' incidence of cancer stage. As demonstrated from results captured in the review by Tarhini *et al.*, differences in incidence rates are observed based on the AJCC staging criteria used. Overall, an increase in incidence was shown regardless of staging criteria (7th edition vs 8th edition AJCC); however, a significant number of patients were reclassified in a higher stage III subgroup under 8th edition criteria [12]. These results could suggest movement toward a lower threshold for higher grade diagnoses over time. Notably, when assessing the different AJCC staging criteria used across longer timeframes over all studies, it becomes increasingly challenging to decipher trends.

Five-year DSS or MSS rates for stage II CM ranged from 63 to 81% and from 36 to 63% for the stage III. The ranges could be explained by variation in treatments given to patients. Chi *et al.* reported that surgical intervention and the use of adjuvant therapies were significant prognostic factors for patients with stages I–III melanoma [49]. Other reported factors known to influence survival rates include treatment era, adverse population characteristics and age [37,43,46].

Survival rates were generally reported from large registry data and single-center databases. It is likely that the same patient population was captured in different studies in this review, due to geographical and time period crossover. Additionally, when comparing across studies, different study populations had varying levels of substage breakdown reported, with some publications not reporting these data subsets at all.

Regarding patient survival as an outcome, conditional survival estimates may be an effective approach to account for changes in patient risk profiles over time, in order to more accurately predict longer-term survival. Bowles *et al.* reported an increase of 44% in 5-year DSS from time of diagnosis to 5 years post-diagnosis when applying this method [32].

Ultimately, for studies reporting survival and mortality, heterogeneity in the clinical characteristics and in the reporting of interventions patients received significantly limited comparison of outcomes, making it difficult to draw meaningful conclusions from the existing literature.

Conclusion

Overall, the aim of this review was to gain further insight into the epidemiology of stages II and III CM, as these outcomes inform clinical burden of the disease in this patient population. We have been unable to gain conclusive knowledge in this area or identify meaningful trends due to reporting limitations (specifically the reporting of incidence data). Further, this review highlights a gap in published research on the epidemiology of stages II–III CM. Ultimately, the findings presented here provide a platform for the planning of relevant studies that will generate detailed evidence to inform the treatment and management of stages II and III CM.

Future perspective

We predict that melanoma research will continue to evolve rapidly to keep pace with advancements in treatment of the disease. Currently, published epidemiological studies in stages II and III CM are lacking and much of the available data cannot be used to determine trends. Efforts to support the development of high coverage cancer registries are paramount to developing the evidence base for interventions with potential for better disease management. Comprehensive records including patient stage at diagnosis are required. The healthcare sector has a responsibility to collect data that will accurately inform national and regional population-based registries and the implementation of mandatory reporting would encourage quality coverage.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/mmt-2019-0022

Author contributions

R Miller, I Shui, A Brandtmüller, E Scherrer and K Cadwell were involved in the conception, design and planning of the study; R Miller was responsible for acquisition of the data; R Miller and S Walker were responsible for data analysis; I Shui and K Cadwell also carried out data interpretation. R Miller drafted the manuscript and all authors were involved in critical review and manuscript revisions. The final manuscript was approved by all authors.

Financial & competing interests disclosure

I Shui and E Scherrer are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. A Brandtmüller is an employee of MSD: Pharma Hungary Ltd. R Miller, S Walker and K Cadwell are employees of PHMR Ltd and were contracted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA to perform this systematic review. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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