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Recurrence and survival of melanoma stage I and II in Western countries: a systematic review and meta-analysis

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Recurrence and survival of melanoma stage I and II in Western countries: a systematic review and meta-analysis

Foreword:
I would like to express my heartfelt gratitude to my supervisors, Pål Joranger (PJ), Associate Professor at the Faculty of Health Sciences, OsloMet, and Lill Tove Nilsen (LTN), Researcher and Senior Optical Radiation Adviser at the Norwegian Radiation and Nuclear Safety Authority, for their unwavering support, expert guidance, and invaluable feedback throughout this journey. A big thank you is also extended to librarian Linn Kristine Kristensen at the University Library of Oslo Metropolitan University.

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Abstract

Background: Melanoma is the most rapidly increasing cancer in white populations in Western countries. This systematic review aimed to evaluate the recurrence and survival rates of stage I and II melanomas, and identify the factors associated with increased recurrence and decreased survival rates.

Method: A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. The search included the databases MEDLINE, Embase, and CINAHL, with the latest update in June 2023. Eligible studies included those reporting stage-specific recurrence and survival data for melanomas stage I and II, with focus on Western countries with comparable surgical techniques. Meta-analyses were employed to estimate recurrence rates, as well as disease-free survival (DFS) and overall survival (OS). DFS and OS data were extracted from included studies' Kaplan-Meier curves using a digitalization software.

Results: A total of 12 longitudinal studies, presented in 17 articles, met the inclusion criteria. Among these, 10 studies were included in the subsequent meta-analyses (random-effects model). The analysis comprised 14,312 participants receiving treatment from 1981 to 2014, with a median follow-up duration ranging from 1.25 to 16 years. Of the included studies, five were RCTs, two employed a quasi-experimental design, and five were cohort studies. The results of the meta-analyses showed a pooled recurrence rate for any recurrence (95% CI) in stage I melanomas of 14.5% (9.6-19.7) and 35.2% (28.7-42.5) for stage II. The 5-year pooled DFS (95% CI) for stage I and II were 84.4% (81.4-87.5) and 61.4% (56.0-66.6), respectively. The 5-year pooled OS (95% CI) for stage I and II were 90.4% (86.5-93.4) and 70.4% (61.9-78.2), respectively. There is great uncertainty associated with the presented estimates, particularly concerning recurrence, where the estimates from different studies show considerable variation. Several clinicopathological characteristics, such as increased thickness, high age, presence of ulceration, male gender, and the location of the melanoma, exhibited significant implications on recurrence, DFS, and OS.

Conclusion: This review indicates an increase in mortality and recurrence as melanoma advances, and a co-variation between ulcerations and advanced stage. Variations in recurrence, DFS and OS rates is found, owing to different classifications, study design and populations, ultimately complicating comparisons. There is a need for meta-analyses based on population-based studies in Western countries that include both stage-specific recurrence and survival data using a common staging system.

Keywords: Melanoma, Recurrence, Survival, Western countries, Stage

Sammendrag

Bakgrunn: Melanom er den krefttypen som øker raskest i hvite befolkninger i vestlige land. Denne systematiske oversikten hadde som mål å evaluere tilbakefalls- og overlevelsesrater for melanomer i stadium I og II, og identifisere faktorer knyttet til økte tilbakefalls- og reduserte overlevelsesrater.

Metode: En systematisk gjennomgang og metaanalyse ble utført med utgangspunkt i PRISMA 2020. Søket inkluderte databasene MEDLINE, Embase og CINAHL, med den siste oppdateringen i juni 2023. Kvalifiserte studier inkluderte de som rapporterte stadium-spesifikke tilbakefalls- og overlevelsesdata for melanomer stadie I og II, med fokus på vestlige land med sammenlignbare kirurgiske teknikker. Metaanalyser ble benyttet for å estimere tilbakefallsrater, samt sykdomsfri overlevelse (DFS) og total overlevelse (OS). DFS- og OS-data ble ekstrahert fra inkluderte studiers Kaplan-Meier-kurver ved bruk av programvare for digitalisering.

Resultater: Totalt 12 longitudinelle studier, presentert i 17 artikler, oppfylte inklusjonskriteriene. Av disse ble 10 studier inkludert i den påfølgende metaanalysen (random model). Analysen omfattet 14 312 deltakere som mottok behandling fra 1981 til 2014, med en median oppfølgingsvarighet som spenner fra 1,25 til 16 år. Av de inkluderte studiene var fem RCT'er, to hadde kvasi-eksperimentelle design, og fem var kohortstudier. Resultatene fra metaanalysen ga en gjennomsnittlig total tilbakefallshyppighet (95% KI) for stadium I melanomer på 14,5% (9,6-19,7) og 35,2% (28,7-42,5) for stadium II. De 5-årige kombinerte DFS-prosentene (95% KI) for stadium I og II var beregnet til henholdsvis 84,4% (81,4-87,5) og 61,4% (56,0-66,6). De 5-årige kombinerte OS-prosentene (95% KI) for stadium I og II var beregnet til henholdsvis 90,4% (86,5-93,4) og 70,4% (61,9-78,2). Det er stor usikkerhet knyttet til presenterte estimater, spesielt når det gjelder tilbakefall, der variasjonen mellom studiene synes å være spesielt stor. Flere klinisk-patologiske karakteristikker, som økt tykkelse, økt alder, tilstedeværelse av ulcerasjon, mannlig kjønn og plasseringen av melanomet, ga signifikante konsekvenser for tilbakefall, DFS og OS.

Konklusjon: Studien indikerer økning i dødelighet og tilbakefall etter hvert som melanomet utvikler seg, og samvariasjon mellom ulcerasjoner og avansert stadium. Variasjoner i tilbakefall, DFS og OS-rater oppdages på grunn av ulike klassifiseringer, studiedesign og populasjoner, noe som til slutt kompliserer sammenligninger. Det er behov for metaanalyser basert på populasjonsbaserte studier i vestlige land som inkluderer både stadiumsspesifikke tilbakefalls- og overlevelsesdata ved bruk av et felles stadieinndelingssystem.

Nøkkelord: Melanom, Tilbakefall, Overlevelse, Vestlige land, Stadium

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Background

Melanoma incidence has been steadily increasing for decades in Western regions, including North America, Europe, Australia, and New Zealand (1-3), which collectively contribute to 80% of global melanoma cases (4). In Scandinavian countries, such as Norway, Sweden, and Denmark, there has been a remarkable rise in melanoma incidence dating back more than six decades, with an age-standardized rate per 100.000 (both sexes) varying from 3.1-4.5 in 1960, to a staggering 33.9-43.1 in 2020 (5), making it the fastest-growing cancer in white populations (6). Projections suggest that while some Western countries may experience a slight decline in cases, many will continue to see an increase (1, 3). This concerning trend is primarily attributed to preventable factors, with 90-96% of the rise in incidence linked to ultraviolet (UV) exposure (7).

In Western countries, the majority of melanoma patients, about 85-90%, are initially diagnosed with primary stage I and II disease, indicating no spread to lymph nodes or distant organs (8-10). A significant portion, approximately 60-70%, falls under stage I due to their ≤2.0mm thickness (6, 11-15). More patients die from to stage I melanoma than stage II in absolute numbers (16, 17), emphasizing the significance of research on this substantial and expanding group of primary melanoma patients, and the factors influencing their recurrence and survival outcomes.

Accurate melanoma staging at diagnosis is crucial for guiding treatment decisions and prognostic assessments. The American Joint Committee on Cancer (AJCC) 8th edition staging system is an internationally recognized standard that uses TNM (*Tumor, Node, Metastasis*) classification to determine the tumor's anatomical extent (8, 18). Melanomas in stage I and II vary in width (0.8 mm to >4.0 mm) with ulceration as an important criterion, signifying adverse tumor biology (19, 20). The presence of ulceration is associated with reduced survival, increased tumor thickness, and therefore higher AJCC stage scores (8, 21, 22). See Additional file 3 for visual representations of melanoma stages and TNM categories. Sentinel lymph node biopsy (SLNB) helps detecting nodal micrometastases; the identification of stage III disease, enabling more aggressive surgical interventions or the administration of systemic therapies, with the aim of enhancing outcomes (23).

Stage I and II melanoma treatment involves a wide local excision (WLE) with margins determined by tumor thickness (9). Extensive clinical trials have examined optimal margins for melanomas 0.8-4 mm thick (24-31). A 2009 Cochrane review primarily based on

prospective data supports avoiding margins exceeding 2 cm (9). While excision margin recommendations vary slightly among Western countries, there is consensus on the following guidelines: 2.0-5.0 mm for in-situ melanomas, 1 cm for melanomas ≤1 mm thick, 1-2 cm for melanomas 1.01-2.0 mm thick, and 2-3 cm for melanomas 2.01 mm or thicker (9, 32-35).

Stage III and IV melanomas signify advanced disease with lymph node or distant organ involvement, drastically impacting prognosis (8). Historically, stage IV melanoma resulted in just a few months of median survival (36). The last decade of advancements in systemic therapies, such as immunotherapy or targeted therapy, have led to significant improvements in long-term survival, reaching up to 50% for stage III and IV patients (36-41). However, these treatments come with notable side effects (36), healthcare costs, and a rapidly changing treatment landscape (8). Focusing solely on stages I and II in this review allows for a more concentrated analysis. It helps highlight similarities in melanomas at comparable stages, assess the effectiveness of similar treatments, identify potential risk factors, patterns, and improve outcome reporting accuracy.

For this systematic review, the primary objective and research questions were: (a) What are the pooled estimates of recurrence, and (b) pooled estimates of survival (DFS and OS) in stage I and II melanomas within Western nations characterized by similar surgical techniques and excision margins? In addition, (c) which clinicopathological predictors achieve consensus in terms of their influence on recurrence development and survival outcomes?

Method

The PRISMA guidelines for systematic reviews (42), including the checklist (see Additional file 1.0 and 1.1) and flowchart (Fig. 1), were followed throughout the process. Relevant books on the basic principles of data gathering to the task of producing a comprehensive assessment of existing research (43, 44), were utilized.

The systematic search

A comprehensive and systematic search was conducted in June 2022 by author 1 (GNS) in collaboration with a specialized librarian, covering the databases MEDLINE (Ovid), Embase (Ovid), and CINAHL (EBSCO). MeSH terms and keywords for melanoma (e.g., melanoma, malignant melanoma(s)), interventions (e.g., surgical excision/technique, excision (margin), margin of excision, Breslow(s) depth or thickness), compared with (e.g., tumor-/cancer staging, TNM staging (system), TNM classification(s), neoplasm staging), and outcomes (e.g., (cancer) recurrence(s), recurrent disease, neoplasm recurrence, recurrence rate(s),

recrudescence(s), relapse(s), survival rate, disease-free survival, treatment outcome) were included in the search strategy. For systematic search details, see Additional file 2. An updated and identical search was conducted in June 2023 by author 1 (GNS) and the specialist librarian. This was done to ensure that no new relevant studies were omitted from inclusion. Those excluded initially were excluded once again, without any additional review by any of the authors.

Selection of eligible studies

Studies were considered for inclusion if they fulfilled the following criteria: [1] utilized TNM and/or referred to AJCC cancer stage guidelines (whether newer or older versions) in classifying melanoma [2], have surgical techniques and excision margins that do not deviate significantly from the consensus of other countries [3], studies from Western countries with comparably well-developed healthcare systems [4], were published in English [5], were randomized controlled trials, cohort studies, case studies, or prognostic studies. Reviews and meta-analysis were excluded.

This systematic review will encompass a wide definition of Western countries, including the whole of Europe, North America (e.g. Canada, USA) and Australia and New Zealand, all with relatively advanced healthcare systems. This study will exclusively encompass melanomas situated on the trunk, extremities, head, and neck. Study arms with excision margins significantly deviating from international consensus standards (9), was excluded based on a joint author evaluation (see footnotes [a / b] in Table 3).

An initial review of titles and abstracts was carried out by author 1 (GNS)[1]. Subsequently, a full text review of the 19 remaining search results was carried out by author 1 (GNS), and in addition split between author 2 (LTN) and 3 (PJ) (see Fig. 1). All disagreements on eligibility were resolved via discussion and review by the third author.

Assessing the quality of the studies

We evaluated 19 quantitative studies using customized checklists, inspired by the Critical Appraisal Skills Programme (CASP) guidelines for RCTs (45) and cohort studies (46). The adjustments aimed to address factors relevant to our data extraction. We assessed seven RCTs and studies comparing two sets of excision margins (presented in twelve articles) (25-28, 30, 31, 47-52), along with twelve cohort studies (12, 29, 53-62).

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[1] Please refer to page 35 for comments from the main supervisor (PJ).

Table 1. Quality assessment criteria utilized.

Cohort studies		Randomized controlled trials and studies comparing two sets of excision margins	
[1]	a clearly focused research question	[1]	a clearly focused research question
[2]	an acceptable recruitment strategy	[2]	an acceptable recruitment strategy and the assignment of participants into intervention groups were randomized
[3]	the participants are representative of the population with melanoma	[3]	the participants are representative of the population with melanoma
[4]	an accurate measurement of exposure to minimize bias	[4]	the study groups were similar at the start of the randomized controlled trial
[5]	an accurate measurement of outcome to minimize bias	[5]	an accurate measurement of outcome to minimize bias
[6]	identifying all important confounding factors and accounting for them in design and analysis	[6]	all participants, regardless of study group, received the same level of care
[7]	a complete follow up of the participants	[7]	a complete follow up of the participants and all participants who entered the study were accounted for at its conclusion

To ensure validity and reduce bias, two authors (GNS/LTN and GNS/PJ) independently assessed each included study (43, 44). We employed checklists (see Table 1) that were summarized into a total score, where 7 indicated high quality, 5-6 represented moderate quality, and a score below 5 was considered low quality, as shown in Table 2.

Data collection process

Table 3 summarizes key features of the included studies for easy reference and analysis. Information extracted from each study includes author(s), publication year, data collection period, study location, sample size, median follow-up, tumor thickness, excision margin, and study-specific outcome measurements. In cases of multiple publications from the same trial, the most comprehensive and current data were utilized.

Table 4 categorizes recurrent melanoma disease percentages and survival rates (DFS and OS) by melanoma staging, and its pooled effect size (PES) with a confidence interval of 95%. Due to variations in initial melanoma size, the staging included four divisions: stage IA+B (stage I), stage IB only, stage IB-IIA-C, and stage IIA-C (stage II). This classification allowed for meaningful outcome comparisons across studies and patient groups.

Relevant clinicopathological characteristics across all studies were thoroughly examined, including age, gender, tumor thickness, stage, ulceration, excision margin, tumor site (trunk, lower extremity, upper extremity, head-neck), recurrence site, histogenetic type, Clark level of invasion, median time to recurrence, sentinel lymph node pathology, and mitotic rate. Data

relevant to these variables were analyzed for their associations with overall survival (OS), disease-free survival (DFS), local, regional, in-transit, lymph node recurrences (LR), and distant recurrence (DR), and their statistical significance was assessed. Significant findings, with p-values < .05 (44), are presented in Table 5, contributing to the exploration of clinicopathological consistency among the studies.

The task of data compilation for Table 3, 4, and 5 was undertaken by author 1 (GNS), and the accuracy and reliability of the extracted information were ensured by an independent verification process conducted by author 2 (LTN) and 3 (PJ).

Analysis of recurrence rates

In our analysis of PES for different forms of recurrence, we focused on individuals with treated melanoma in stage I and II (see Table 4). Our primary concern was the proportion of individuals experiencing relapse.

While most meta-analyses are conducted to estimate PES for interventions, where the relevant effects might be absolute risk reduction, relative risk, odds ratio (OR), or weighted or standardized mean difference, meta-analysis methods can also be employed to obtain a more precise estimate of disease occurrence and prevalence rates (63). One common issue in the studies we summarized is that most lack estimates of uncertainty (CI, SD, SE, or p-values) for both recurrences, DFS, and OS. To address this challenge and the need for data transformations, we relied on Barendregt et al. (63) as the basis for our meta-analyses. Here, we define recurrence as a proportion, estimated by the number of cases of melanoma in a sample divided by the sample size, resulting in a prevalence between 0 and 1, following a binomial distribution.

Many commonly used meta-analysis methods are based on the inverse variance method (or modifications thereof). The binomial equation for variance (expressed as a proportion) can be used to estimate SE and consequently the weights for different studies. Refer to equations 1-4 in Barendregt et al. (63) for the estimation of these variances using the "inverse variance method." This method works well for prevalence proportions around 0.5. However, if the proportion of recurrence approaches the boundaries in the range of 0 to 1, the method can become problematic. For example, if the proportion is very small, one study can have a disproportionately large weight when using the inverse variance method. To correct for this, we employ the 'double arcsine transformation´. Proportions and their corresponding standard

errors transformed via the double arcsine transformation are subsequently used in meta-analyses employing random methods to estimate PES.

We use the random method in Table 4 to account for between-study variability and provide more conservative estimates that incorporate the inherent heterogeneity among the included studies (43). As a sensitivity analysis of how the methods affect our calculated PES, we compared these for both random and fixed methods, and with simple means (adding the percentages and dividing by the number of percentages) and weighted means (using the samples size of the various studies) in Additional file 4.0-4.1.

In Additional file 5.0, an example spreadsheet is provided to illustrate transformations (example given is 2-year DFS for stage II - the same transformations and meta-analysis methods described are applied for all the analyses of recurrences, DFS, and OS). Simple measures of PES for the included studies are also presented by calculating unweighted mean and by calculating weighted averages with corresponding confidence intervals (weights are based on sample sizes).

Analysis of DFS and OS

One challenge with recurrence estimates is the potential impact of sample dropout, which might artificially lower recurrence rates. However, our DFS and OS analyses, using Kaplan-Meier survival curves, address this issue. Data on DFS and OS from included studies were extracted using the web-based tool WebPlotDigitizer (64), which enabled the accurate digitization of Kaplan-Meier curves (12, 25, 27, 28, 31, 48, 49, 52, 55, 58), reducing the potential for manual transcription errors. The extracted data is also presented in tabular format in Table 4. As for the estimation of the pooled results for recurrence, we also assume a binomial distribution for our pooled estimates for DFS and OS.

It's important to note that not all studies provide follow-up data up to the 10-year mark, leading to variations in the combined analyses at 2, 5, and 10 years. In some cases, 10-year OS may exceed 5-year OS. Therefore, 2, 5, and 10-year OS and DFS estimates should be interpreted as single estimates and not as parts of a continuous OS or DFS survival curve. To better handle this challenge, we have presented OS and DFS in the form of survival curves (Figs. 2a-5a).

The pooled mean (weighted or unweighted) of OS and DFS based on Figs. 2a-5a, share the same limitation as discussed earlier for point estimates. At specific time points, these pooled curves may exhibit increments, making them unsuitable as OS or DFS survival curves (see

examples in Additional file 6.0). To address this, we combined the curves whenever data were available, but without allowing the pooled proportion of survivors to increase over time. Here is how: Let us assume year 5 is the last year with data in all the pooled studies. From year 5 to year 6, we adjusted the combined curve by a percentage point, following the percentage change observed in graphs with data for both 5 and 6 years. This process was repeated for year 6 to 7, and so on. This approach created a pooled curve that simulates an approximation of a survival curve. Here we assume that graphs that "stop" would, in terms of proportions, follow the same pattern the following years as the graphs still having data. In the results chapter, Figs. 2b-5b, we present these pooled and adjusted graphs based on both unweighted and weighted averages using sample sizes. In Additional file 4.2, we compare the results from using unweighted mean, weighted mean, meta-analysis fixed-effects model (using transformed data), and meta-analysis random-effects model (using transformed data).

The pooled average mean curves provide a straightforward representation of OS and DFS across the included studies, giving equal weight to each study regardless of its sample size or statistical power, offering a more intuitive view of the general direction of the data. The pooled weighted mean curves considers the sample size of each study, assigning greater weight to larger studies (44). Due to variations in data quality, sample size and importance in the included studies, an elaboration on the weighted mean will be provided.

The responsibility for extracting data on DFS and OS from the Kaplan-Meier curves in the studies using WebPlotDigitizer was evenly distributed among all three authors. All digitalized graphs were controlled against the graph in the articles by another author.

Out of the 12 studies included in this review, 10 studies provided data that were relevant for inclusion in a meta-analysis (12, 25, 27, 28, 31, 49, 55, 57, 58, 62). Data on types of recurrence from the original articles underwent a thorough reevaluation, by all three authors, to identify and rectify any potential transcription errors before their utilization.

Forest plots were developed following Cooper's step-by-step approach (43) and using the STATA version 18 software and manual (65). The pooled effect rates for recurrence, DFS, and OS, along with their corresponding 95% confidence intervals, were computed and are presented in Table 4.

Heterogeneity among the included studies was assessed using I^2-values in the meta-analyses. I^2 quantifies variability among the studies: low values indicate study similarity and consistent results, while high values suggest significant variability due to methodological or clinical

differences, potentially leading to inconsistent results. The reference range is 0-100%, with a tentatively 25% indicating low, 50% moderate, and 75% high heterogeneity (66). The meta-analysis focused exclusively on stages I and II, excluding stage IB and stage IB-IIA-C (refer to table 4), as their classifications were unclear. Forest plots were generated (see Additional files 4.0, 4.1, and 4.2) to visually display effect estimates for different recurrence rates, DFS, and OS. These plots illustrate the variability around each study's estimate, the study weights in the meta-analysis, and the overall outcomes from all included studies (67).

Meta-analyses were also conducted in three subgroups within the various recurrence categories (see Additional file 4.3). These subgroups compared studies in terms of [1] data collection timing (differentiating between newer and older research based on the median year of data collection, using a cutoff of the year 2000), [2] median years of follow-up (differentiating between long and short follow-up based on a threshold of 5 years), and [3] quality assessments of the included studies (categorized as moderate or high quality, as shown in Table 2). The significance level for testing group differences was set at $p < 0.05$ (44).

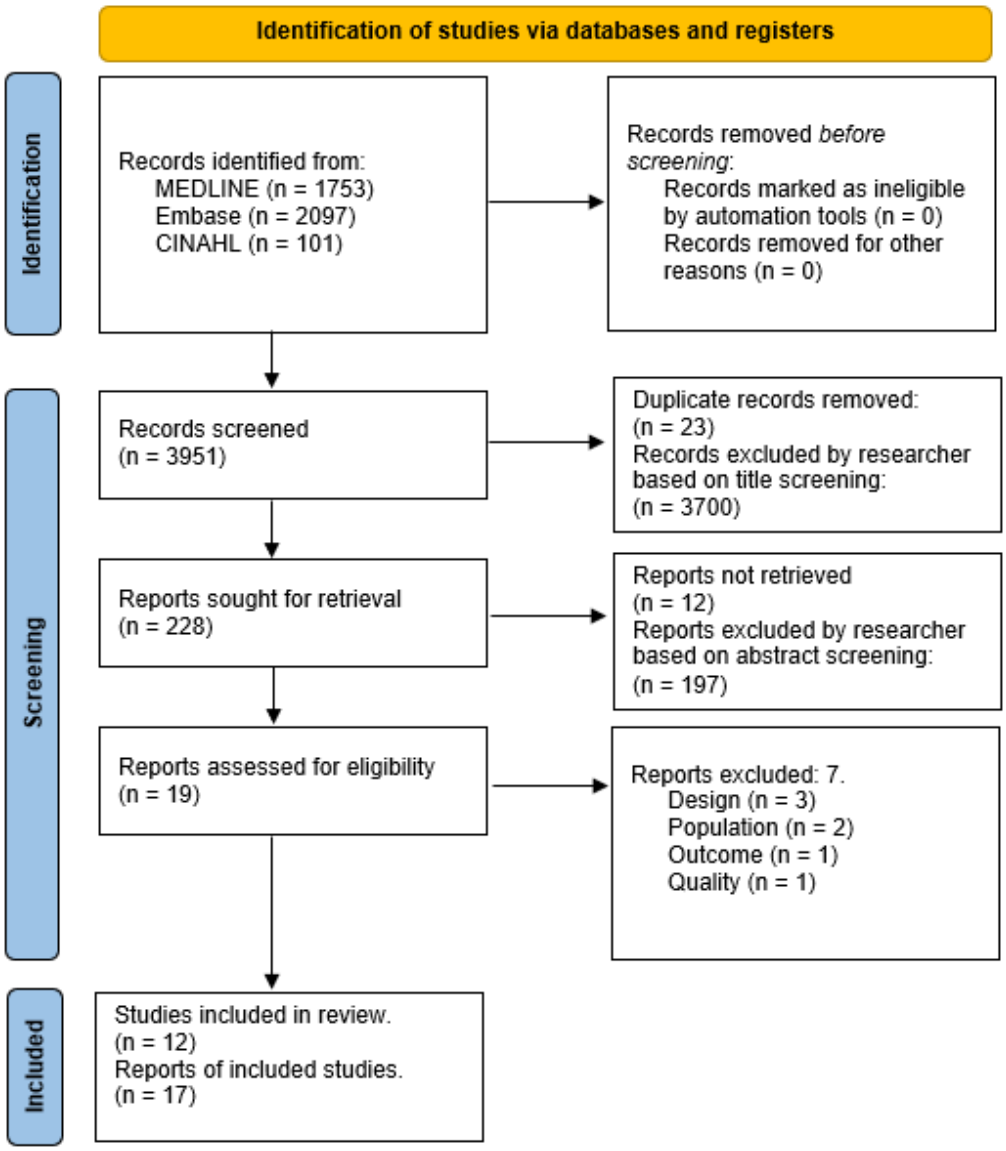

Fig. 1. PRISMA 2020 flow diagram for systematic reviews (42)

Results

Initially, 3951 articles were identified from the databases. After eliminating 23 duplicates and excluding 3700 articles based on title screening, 228 articles underwent retrieval and abstract screening. Subsequently, 19 studies were subjected to full-text eligibility assessment, as depicted in Fig. 1. Out of the 19 studies assessed for eligibility, seven were excluded, leaving a total of 12 studies for inclusion (Table 2). No additional relevant articles were identified during the updated searches conducted in June 2023 by author 1 (GNS) and the specialist librarian.

The combined sample consisted of 14 312 individuals spanning both disease stages, treated between 1981 and 2014. The studies followed a longitudinal design with median follow-up periods ranging from 1.25 to 16 years. Data from twelve countries across the Western world is represented, namely Sweden, Denmark, Norway, Estonia, USA, Canada, France, Poland, UK, Switzerland, The Netherlands, and Australia (Table 3). Two of the included studies encompass study clinics located in South Africa (26, 31, 47, 48, 50). However, the predominant number of participants and the leadership of these studies are centered in Western countries, and therefore included.

Results of the quality assessment

Only studies considered to be moderate or high in quality are included in this review (Table 2). The quality assessment process excluded seven reports, leaving twelve studies included. Exclusion of studies was due to deficiencies concerning design (54, 59, 60), population (53, 56), outcome (61) or quality (30) (refer to Additional file 7.0 for elaborations). All seven studies were excluded after a thorough review and discussion among all three authors. Among the twelve included studies, five were randomized controlled trials (RCTs), two were quasi-experimental studies that compared two different sets of excision margins, and the remaining five studies were cohort studies (Table 3). The studies featured in a total of seventeen reports, presented in Table 3 (12, 25-29, 31, 47-52, 55, 57, 58, 62).

Table 2. Quality assessment of included studies.

Reference	**Criteria**							**Tot**	**Quality**
	1	2	3	4	5	6	7		
Cohn-Cedermark/Ringborg **(25, 51)**	+	+	+	+	+	+	+	7/7	High
Dalal **(55)**	+	+	+	+	+	+	+	7/7	High
Doepker **(29)**	+	+	+	+	+	+	+	7/7	High
Gillgren/Utjés **(28, 52)**	+	+	+	+	+	+	+	7/7	High
Hunger **(49)**	+	+	+	-	+	-	+	5/7	Moderate
Balch/Karakousis/Balch **(26, 47, 50)**	+	+	+	+	-	+	+	6/7	Moderate
Khayat **(27)**	+	+	+	+	+	+	+	7/7	High
Lee **(57)**	+	+	+	+	+	-	+	6/7	Moderate
Leeneman **(58)**	+	+	+	+	+	-	+	6/7	Moderate
Rockberg **(12)**	+	+	+	+	+	+	+	7/7	Moderate
Thomas/Hayes **(31, 48)**	+	+	+	+	+	+	+	7/7	High
von Schuckmann **(62)**	+	+	+	+	+	+	-	6/7	Moderate

(+) and (-) indicates whether criteria were met or not. Studies with high quality=7, moderate=5-6, low <5.

Table 3. Main characteristics of included studies.

	Patients enrolled	Treatment arm, Narrow/Wide Excision	Trial characteristics	Period of data collection	Median follow-up, y	Tumor thickness included	Excision margin	Outcome assessed
Randomized controlled trials								
Swedish MSG Trial Ringborg (1996) **(51)** Cohn-Cedemark (2000) **(25)** Sweden	989	476/513	Prospective multicenter open-label trial. Included primary melanoma located on trunk and limb. Excluded melanoma of the hands and feet, patients with satellites, metastatic disease, or previous malignant disease (except BCC). Surgical treatment was to be performed within 6 weeks. SLNB not implemented.	1982-1991	5.8 (OS) 4 (DFS) 11 (OS) 8 (DFS)	>0.8- ≤2mm	2cm/5cm[b]	Overall survival Disease-free survival Local-, regional skin-, regional node- & distant recurrence New primary melanoma Death
Swedish/Danish MSG Trial Gillgren (2011) **(28)** Utjés (2019) **(52)** Sweden, Denmark, Estonia, and Norway	936	465/471	Prospective multicenter and multinational open-label trial. Included primary melanoma located on trunk or upper or lower extremities in patients ≤75 years of age. Excluded melanoma of the hands and feet, head and neck, anogenital region, previous melanoma or other malignant disease (except BCC and in situ carcinoma of the cervix uteri). SLNB implemented (in 9%) at the end of data collection.	1992-2004	6.7 10	≥2mm	2cm/4cm[b]	Overall survival Disease-free survival Disease-specific survival Local-, regional skin-, regional node- & distant recurrence Death
Intergroup Trial Balch (1993) (a) **(47)** Karakousis (1996) (a+b) **(50)** Balch (2001) (a+b) **(26)** USA, Canada, Denmark, and South Africa	468 (a) 740 (a+b)	238/230	Prospective multicenter and multinational open-label trial. Included primary melanoma on (a) trunk or proximal extremity (N=468), and (b) distal extremity, head and neck (N=272). Patients with previous cancer (except skin cancer), who received chemo/radiotherapy, or had lentigo maligna melanoma, were excluded. Elective Lymph Node Dissection or observation assigned randomly.	1983-1992	6 7.6 10	1-4mm	2cm/4cm[b] (a) & 2cm only (b)	Overall survival Disease-free survival Disease-specific survival Local-, in-transit-, regional- & distant recurrence Rate of skin graft Wound infection/dehiscence
European/French Trial Khayat (2003) **(27)** France	326	161/165	Prospective multicenter and multinational open-label trial. Included primary melanoma in patients ≤70 years of age. Melanoma of the toe, nail, finger and arising from melanosis, lentigo, and acral lesions, were excluded. SLNB not implemented.	1981-2000	16	≤2mm	2cm/5cm[b]	Overall survival Disease-free survival Local-, regional node- & distant recurrence Death
UK MSG Trial Thomas (2004) **(31)** Hayes (2016) **(48)** UK, Poland, and South Africa	900	453/447	Prospective multicenter and multinational open-label trial. Included primary melanoma in patients ≥18 years of age, located on the trunk or limbs (not soles of feet or palms of hands). Pregnant women, previous malignant disease, or patients on immunosuppressive medications, were excluded. SLNB not implemented.	1992-2001	5 8.8	≥2mm	1cm[a]/3cm	Overall survival Disease-free survival Melanoma-specific survival Local-, in-transit-, regional node & distant recurrence
Quasi-experiment comparing two sets of excision margins								
Doepker (2016) **(29)** USA	965	302/663	Retrospective single center database analysis of primary melanomas, all given 1 or 2 cm excisions. Patients who underwent re-excision after melanoma in situ or with involved margins were excluded. SLNB not performed in	2002-2013	1.25	1.01-2mm	1cm/2cm	Overall survival Disease-specific survival

			100 patients due to patient preference, comorbid conditions, or failure to map.					Local-, regional node or in-transit- (w/patterns) & distant recurrence Wound closure Predictive factors for LR
Hunger (2015) **(49)** Switzerland	325	228/97	Retrospective single center database analysis of primary melanoma, all given 1 or 2cm excisions. Patients without documented surgical margins or follow-up were excluded. SLNB were performed in all patients.	1995-2012	5	≥2mm	1cm[a]/2cm	Overall survival Disease-free survival Local-, locoregional- & distant recurrence Death
Cohort studies								
Dalal (2007) **(55)** USA	1046	NA	Retrospective single center database analysis of primary melanomas, all given SLNB. ≥1.0mm melanomas, or high-risk primaries with ulcerations and/or major regression, were included. Patients with multiple primary tumors who underwent SLNB in multiple basins, or those with clinical stage III, were excluded.	1991-2004	3	≥1mm	WLE	Disease-free survival Post-recurrence survival Local-, in-transit-, nodal- & systemic recurrence Site recurrence x variables
Lee (2017) **(57)** USA	738	NA	Retrospective single center database analysis of stage IIA (n=400), IIB (n=226) and IIC (n=112) primary melanomas, uncovering patterns and timing of initial recurrence. All patients underwent SLNB.	1993-2013	4.3	≥1- >4mm	NA	Disease-specific survival Site of & time to recurrence Method of detection Local/in-transit-, nodal- & systemic recurrence Death
Leeneman (2019) **(58)** The Netherlands	3093 /1397	NA	Retrospective observational cohort study in six hospitals using data from a national cancer registry of stage IB, II and III melanomas in detecting survival (n=3093) and disease recurrence and post-recurrence survival (n=1397). SLNB is not discussed in the study.	2003-2011	5.4	≤1- >4mm	NA	Overall survival Post-recurrence survival Disease-free survival Time to first recurrence Local-, intralymphatic-, regional node- & distant recurrence
Rockberg (2016) **(12)** Sweden	3554	NA	Population based retrospective epidemiologic analysis of stage I-IV melanoma in Stockholm County. SLNB not performed systematically.	2005-2012	4.4	≤1- >4mm	NA	Overall survival Disease-free survival Time to recurrence Total recurrence Predictive factors
von Schuckmann (2019) **(62)** Australia	700	NA	Prospective multi-center cohort study in stage IB-IIC primary high-risk melanomas. All patients ≥16 years of age and able to complete the study questionnaire were included. SLNB performed in 36.9%.	2010-2014	2	≤1- >4mm	WLE	Disease-free survival Local-, regional- & distant recurrence Risk factors for recurrence

MSG = Melanoma Study Group, WLE = Wide Local Excision, not defined further, NA = Not applicable, [a / b] = Narrow/wide excision margins used in this study are not in consensus with recommended guidelines **(9)**

DFS and OS results

The estimated pooled OS graph based on pooled weighted means in stage I is 98% (2y), 92% (5y), 86% (10y), and 81% (15y) (Fig. 2b), compared to 87% (2y), 67% (5y), 48% (10y), 36% (15y), and 30% (20y) in stage II (Fig. 4b). The pooled OS graph based on unweighted means exhibit a similar trend in both stages. Mortality decreases over time in both stages. The graph for stage I and II shows a tendency to level off, with a decrease of 14% and 52% in the first 10 years respectively, compared to only 7% and 18% in the following 8 (stage I) and 10 (stage II) years. This is despite the background mortality increasing over time. Stage I has higher overall survival rates compared to stage II at all time points.

The estimated pooled DFS graph based on pooled weighted means (Fig. 3b) in stage I is 94% (1y), 92% (2y), 86% (5y), 68% (10y), and 63% (15y) compared to 84% (1y), 72% (2y), 57% (5y), 48% (8y), and 48% (10y) in stage II (Fig. 5b). The pooled DFS graph based on unweighted means exhibit a similar trend in both stages. In stage I, the graph shows a 32% reduction in DFS at 10 years, which then levels off with only an additional 7% reduction 8 years later. Stage II has data for only 10 years, but it indicates a tendency to level off earlier, with a 43% reduction in DFS in the first 5 years, compared to only an additional 9% reduction at 10 years. Stage I patients consistently have higher DFS rates compared to Stage II patients at all time intervals.

The meta-analysis showed the pooled DFS effect size (95% CI) at 2y, 5y, and 10y to be 93.4 (90.4-95.8), 84.4 (81.4-87.5), 67.6 (56.9-77.4) in stage I, and 74.8 (69.9-79.9), 61.4 (56.0-66.6), 37.6 (29.1-46.5) in stage II. The pooled OS effect size (95% CI) at 2y, 5y, and 10y was calculated to be 97.1 (95.2-98.6), 90.4 (86.5-93.4), 82.9 (76.1-88.5) in stage I, and 88.2 (83.3-92.6), 70.4 (61.9-78.2), 48 (45.5-51.0) in stage II (see Table 4 and Additional file 4.2).

We see that there is a tendency that unweighted means and the random-effects model give similar results, and the same for weighted mean and fixed-effects model (see Figs. 2b-5b and Additional file 4.2).

The form and rate of recurrence

We employed meta-analyses to analyze recurrence (%) rates in subgroups, which include total events, local, in-transit (limited to stage II), regional lymph node, and distant recurrences, within stage I and II melanomas. As shown in Table 4 and Additional file 4.0 and 4.1, the meta-analyses of stage I estimated the total recurrence to be 14.5 (9.6-19.7, I^2=94.7%), local recurrence 0.6 (0.2-1.4, I^2=61.1%), regional lymph node recurrence 5.9 (1.1-14.5, I^2=97.2%),

and distant recurrence 5.2 (4.4-6.4, I^2=4.9%). Further, stage II showed total recurrence to be 35.2 (28.7-42.5, I^2=96.2%), local recurrence 2.4 (1.6-3.6, I^2=69.2%), in-transit recurrence 8.7 (3.4-16.6, I^2=97.5%), regional lymph node recurrence 12.1 (5.7-20.5, I^2=97.8), and distant recurrence 13.1 (9.0-17.4, I^2=93.5). There are relatively large variations in the results of the different articles for the various recurrence outcomes, except for distant recurrence in stage I, and moderate differences regarding local recurrence in both stages.

In the subgroup meta-analysis of various recurrences in stage I and II, no significant differences were found between the groups for [1] data collection year and [3] quality assessments ($p > 0.05$), except for the analysis of [2] median follow-up (± 5 years), which indicated significant group differences ($p = 0.00$) or near significant ($p = 0.06/0.09$) in total any recurrence and regional lymph node recurrence, in both stage I and II. See more on this in Additional file 4.3.

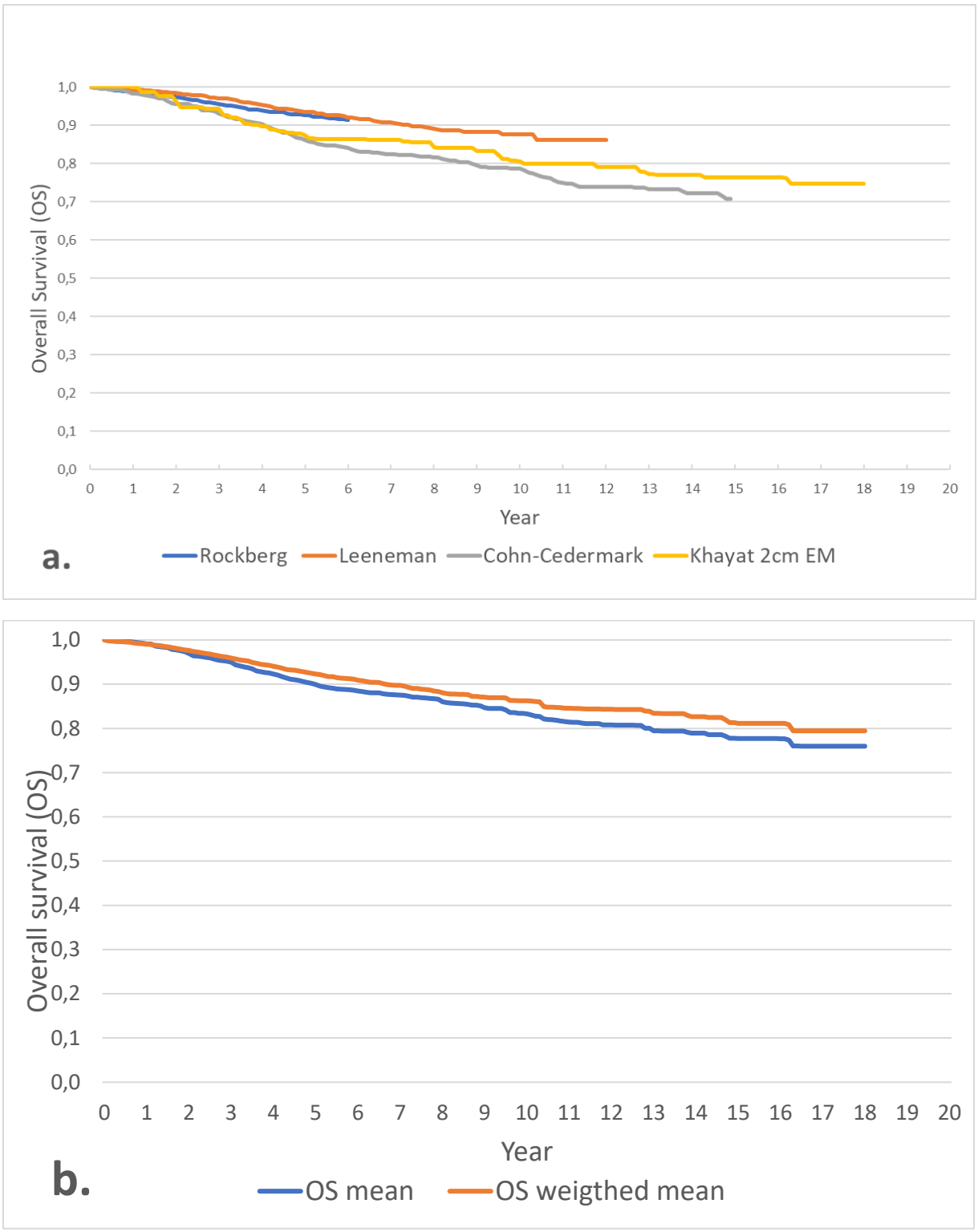

Fig. 2. Overall Survival (OS) in Stage I.
a. Extracted from Kaplan-Meier curves in articles (12, 25, 27, 58).
b. Pooled graph for OS based on pooled means (OS mean) and pooled weighted means (OS weighted means).

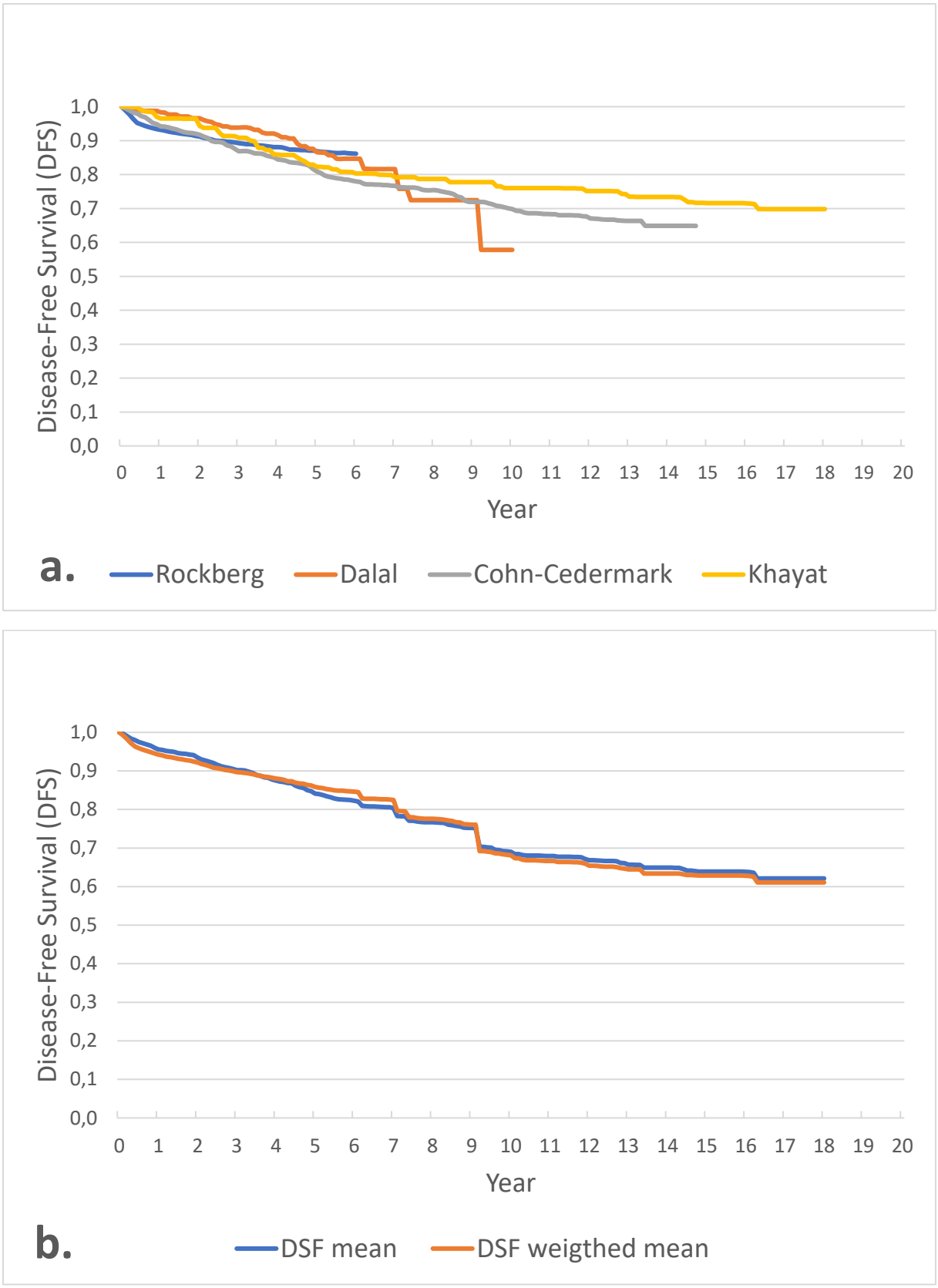

Fig. 3. Disease-Free Survival (DFS) in Stage I.
a. Extracted from Kaplan-Meier curves in articles (12, 25, 27, 55).
b. Pooled graph for DFS based on pooled means (DFS mean) and pooled weighted means (DFS weighted means).

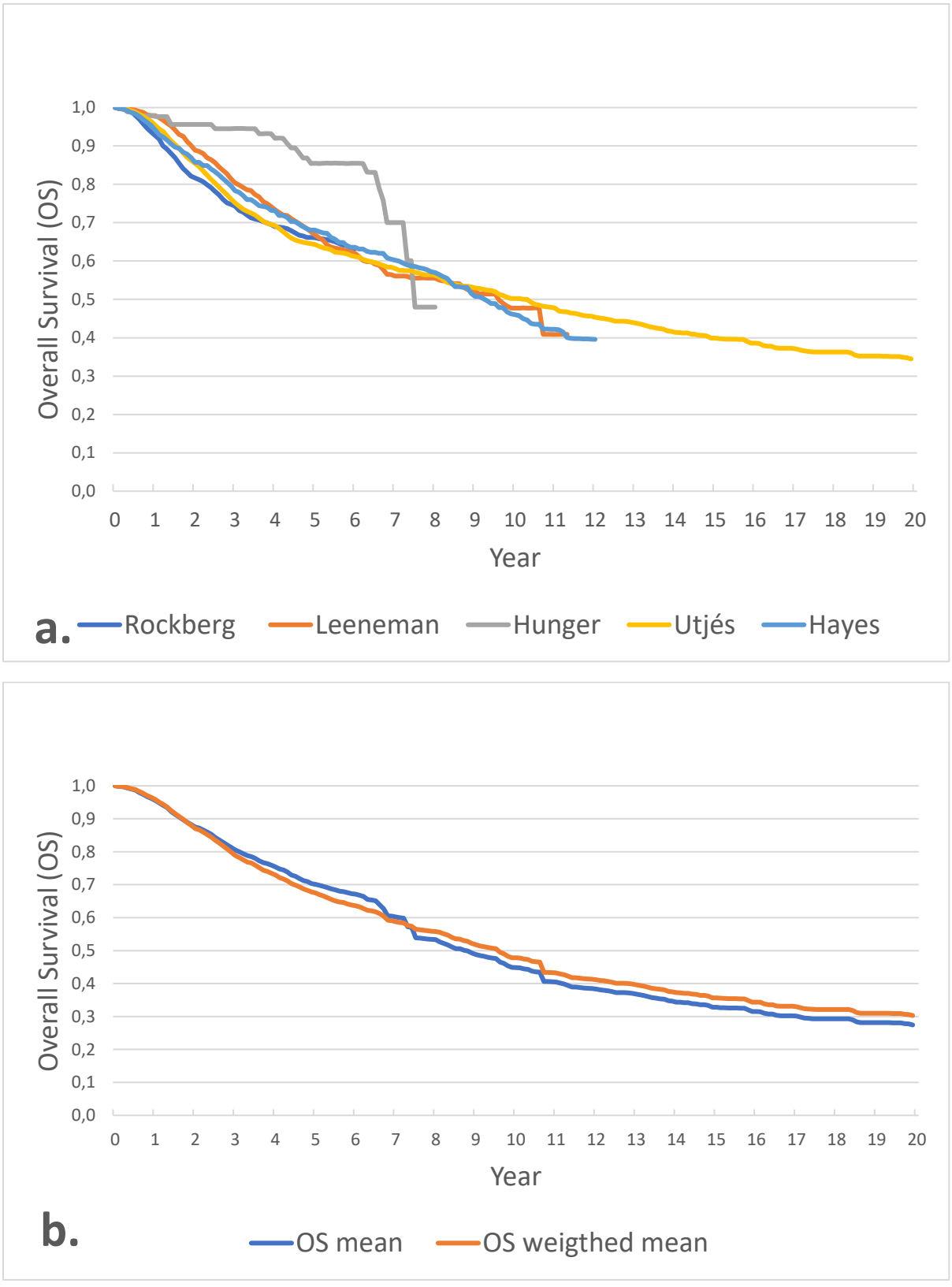

Fig. 4. Overall Survival (OS) in Stage II.
a. Extracted from Kaplan-Meier curves in articles (12, 43, 48, 49, 52, 58).
b. Pooled graph for OS based on pooled means (OS mean) and pooled weighted means (OS weighted means).

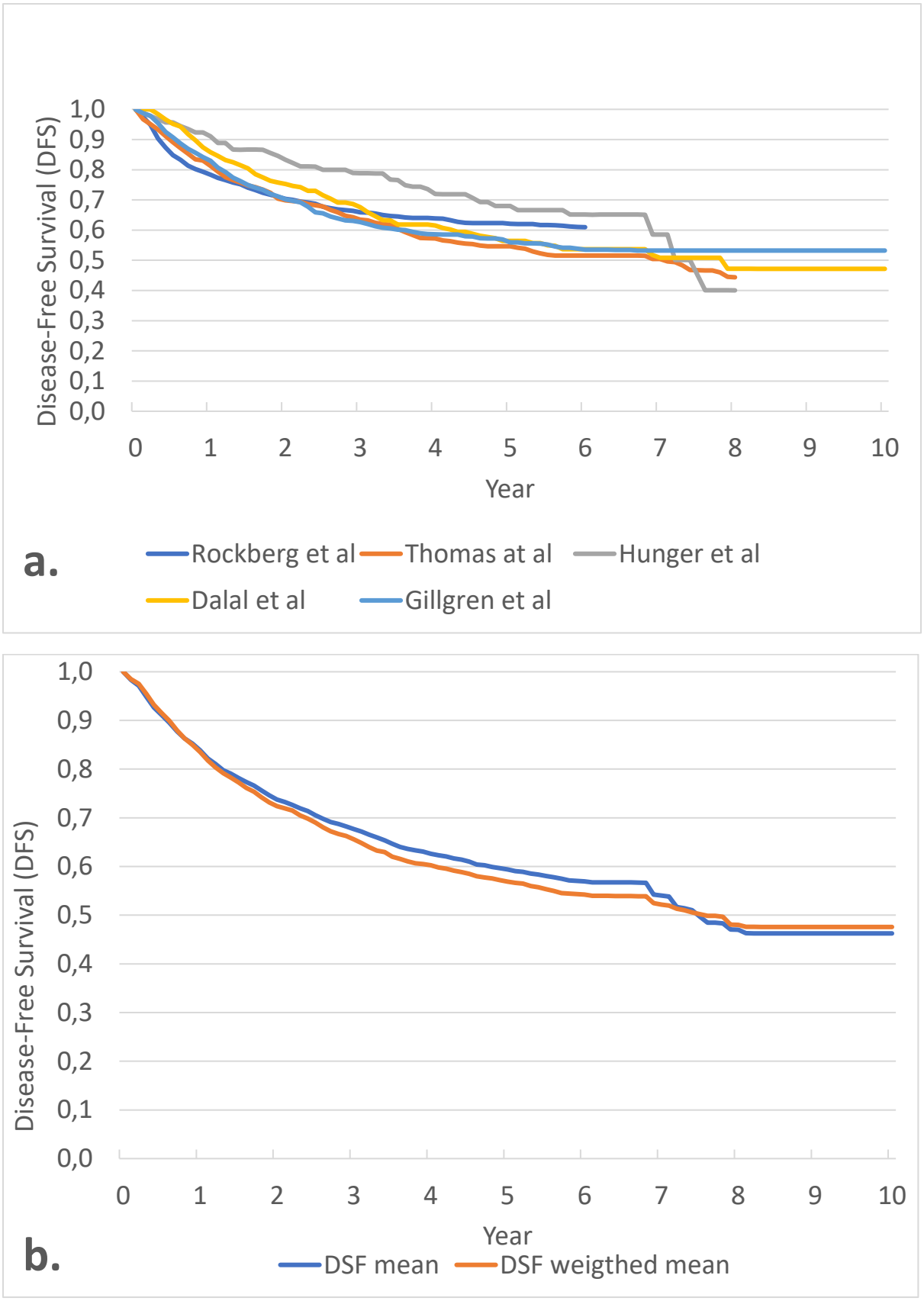

Fig. 5. Disease-Free Survival (DFS) in Stage II.

a. Extracted from Kaplan-Meier curves in articles (12, 28, 31, 49, 55).

b. Pooled graph for DFS based on pooled means (DFS mean) and pooled weighted means (DFS weighted means).

Table 4. Recurrence, DFS and OS in included studies and pooled effect using meta-analysis (random model).

	Study (year)	Stage specific N =	Median follow-up years	Recurrent disease %: Total any event	Local	Regional skin	In transit (Recurrence P-Tumor to R-LN)	Regional lymph node	Distant	Foot-note	Survival %: Disease-free survival (DFS) 2y	DFS 5y	DFS 10y	Overall survival (OS) 2y	OS 5y	OS 10y
Stage IA+B **T1a-T2a <0.8-2.0mm (Ulceration: yes/no, but not in both vertexes)**	Dalal et at. (2007) (55)	561	3	7.7	0.2		1.8	1.1	4.6	h	96.6	86.6	57.8			
	Rockberg et al. (2016) (12)	2523	4.4	14.6						h	91.2	86.9		97.3	92.6	
	Swedish MSG Trial Cohn-Cedermark (2000) (25)	989	8 (DFS) 11 (OS)	19.1	0.5	0.9		11.8	5.9	fh	91.8	80.9	69.8	95.6	86.2	78.6
	European/French Trial Khayat et al. (2003) (27)	326	16	16.9[d]	1.5			7.4	4.3	fh	94.3	82.2	76	96.4	87.5	80.6
	Leeneman et al. (2019) (58)	2299 OS only	5.4											99	93	88
Pooled effect (CI: 95%) Stage IA+B				**14.5 (9.6-19.7)**	**0.6 (.2-1.4)**			**5.9 (1.1-14.5)**	**5.2 (4.4-6.4)**		**93.4 (90.4-95.8)**	**84.4 (81.4-87.5)**	**67.6 (56.9-77.4)**	**97.1 (95.2-98.6)**	**90.4 (86.5-93.4)**	**82.9 (76.1-88.5)**
Stage IB only **T2a >1.0-2.0mm (w/o ulceration)**	von Schuckmann et al. (2019) (62)	352	2	5.7						j	94.3					
	Leeneman et al. (2019) (58)	755 DFS only	5.4	7.5	0.4		1.3	3.2	2.6	h		92.5[j] (5.4y)				
Stage IB-IIA-C **T2a-T4b >1.0->4.0mm (Ulceration: yes/no, but not in first vertex)**	Doepker et al. (2016) (29)	965	1.25	10.9	2.1		4.6		4.2	i				92.3	68.5	
	Intergroup Trial Balch et al. (1993) (47)	740 (a+b)	6							fh				94.6	83.4	
	Karakousis et al.(1996) (50)	468 (a) 272 (b)	7.6	44.9 (a+b)	3.8 (a+b)		6.4 (a+b)	13.3 (a+b)	21.4 (a+b)	fj						
	Location: (a) trunk or proximal extremity 2/4cm EM, (b) distal extremity, head and neck 2cm EM			45.5 (a) 44.9 (b)	4.3 (a+b-2cm) 2.1 (a-2cm) 2.6 (a-4cm) 6.2 (b-2cm)		5.9 (a–2cm) 5.2 (a–4cm) 7.7 (b)	12.8 (a–2cm) 13.5 (a–4cm) 14 (b)	26.4 (a-2cm) 22.3 (a-4cm) 16.9 (b)			75 (a-2cm) 81 (b)			76 (a-2cm) 81 (b)	
	Balch et al. (2001) (26)		10		2.3 (a total) 2.1 (a-2cm) 2.6 (a-4cm) 6.2 (b-2cm)											
Stage IIA-C **T2b-T4b >1.0->4.0mm (Ulceration: present in both mm-vertexes)**	von Schuckmann et al. (2019) (62)	310	2	18.4						j	81.6					
	Dalal et al. (2007) (55)	485	3	33	1.9		8	7.2	15.9	h	75.3	56.5	47.2			
	Lee et al. (2017) (57)	738	4.3	29.7			11.9[e]	6.8	11							
	Rockberg et al. (2016) (12)	746	4.4	39.9						h	70.3	62		81.6	66.1	
	UK MSG Trial Thomas et al. (2004) (31) Hayes et al. (2016) (48)	900	5 8.8	42	3.1		1.9	29.2	7.8	gh	69.8	54.6		85.8	68	46
	Hunger et al. (2015) (49)	325	5	49.9	3.4		22.8		23.7	gh	83.3	68		95.6	85.5	
	Leeneman et al. (2019) (58)	565 (OS) 471 (DFS)	5.4	29.1	0.8		5.3	10.8	12.1	h		70.9[j] (5.4y)		88.9	66.8	47.7
	Swedish/Danish MSG Trial Gillgren et al. (2011) (28) Utjés et al. (2019)	936	6.7 19.6	42.1	3.1*	3.6		22.9	9.8	fh	70.2	56	53.2	85.5	64.3	50.3
Pooled effect (CI: 95%) Stage IIA-C				**35.2 (28.7-42.5)**	**2.4 (1.6-3.6)**		**8.7 (3.4-16.6)**	**12.1 (5.7-20.5)**	**13.1 (9.0-17.4)**		**74.8 (69.9-79.4)**	**61.4 (56.0-66.6)**	**37.6 (29.1-46.5)**	**88.2 (83.3-92.6)**	**70.4 (61.9-78.2)**	**48.0 (45.5-51.0)**

Only the latest and comprehensive reports of the included studies are utilized and presented in this table. [d] = Unknown location of recurrence added to the total events, but not included in the differentiation. [e] = Local/in-transit recurrences combined. [f / g] = Wide / Narrow excision margin utilized in this study deviate from recommended guidelines (9), and consequently not applied. [h] = The figure is extracted from the article's Kaplan-Meier curves using WebPlotDigitizer (64). [i] = Both study arms in this study are pertinent to current clinical practice, and consequently, an average has been computed through the analysis of their Kaplan-Meier curves using WebPlotDigitizer (64). [j] = The figure is specified in the article's text. [*] = p-values are significant, two sets of excision margins are compared.

Clinicopathological variables influencing recurrence and survival

Table 5 presents variables from all the incorporated studies that exhibit statistically significant correlations ($p < 0.05$), or no significant correlations ($p > 0.05$), with overall survival (OS), disease-free survival (DFS), local, regional, in-transit, or lymph node recurrences (LR), and distant recurrence (DR).

The median age in the included studies ranged from 47.7 to 64 years. Four studies (12, 28, 29, 31, 48, 52) reported a significant correlation between increasing age and lower survival rates. Khayat et al. (27) found no significant impact of age on OS, likely due to the younger population included (mean age of 44 years), and the exclusion of all patients over the age of 70. The epidemiological analysis of Rockberg et al. from the Stockholm County (12) found a significant correlation between age and increasing recurrence rates (0.7% per year). However, other studies (27, 28, 31, 48, 52, 62) did not report a significant age-related correlation.

Male gender consistently correlates with lower survival rates and a higher incidence of recurrence in most studies (12, 27-29, 31, 48, 52). An exception is the Australian cohort study by von Schuckmann et al. (62), which found no correlation between gender and increased recurrence. It's worth noting that this study had a relatively short median follow-up of 2 years, and differences in the number of recurrence cases between genders were reported (69.1% men, 30.9% women).

An increase in melanoma thickness, indicative of advanced stage, consistently correlates with reduced DFS and OS, with all relevant studies reporting significant findings (12, 26-29, 31, 47, 48, 50, 52, 55, 62). In these studies, ulceration of the melanoma is also consistently associated with reduced OS, except in the cases of Khayat et al. (27) and Rockberg et al. (12), which did not investigate this correlation. Furthermore, all studies show that ulceration significantly impacts recurrence rates, apart from Doepker et al. (29).

In this systematic review, seven out of the twelve included studies explored the impact of different excision margins (9, 25-29, 31, 47-52). The importance of a complete surgical excision margin, is one of the major controversies in the management of primary melanomas stage I and II (27, 68), especially in more advanced cases with thickness exceeding 2 mm (28, 31). Two European RCTs, conducted by Khayat et al. (27) and Cohn-Cedermark and colleagues (25), compared a 2 cm to a 5 cm excision margin in thin melanomas (≤2.0 mm) and found no significant disadvantage in terms of DFS or OS with the use of the narrower excision margin. However, in studies focusing on more advanced melanomas (>2.0 mm) (26,

28, 29, 31, 47-50, 52), the utilization of a narrower 1 cm excision margin was associated with a significantly less favorable OS in the study by Doepker et al. (29) and a significant increase in recurrence rates in the UK Melanoma Study Group trial by Thomas et al. and Hayes et al. (31, 48).

In several studies, including those by Doepker et al. (29), von Schuckmann et al. (62), and the Intergroup Trial by Balch et al. (47), Karakousis et al. (50) and Balch et al. (26), the presence of melanomas in the head and neck region was significantly associated with an increased risk of recurrence. Moreover, it had a significant impact on overall survival in the Intergroup Trial (26, 47, 50). The Swedish/Danish Melanoma Study Group (MSG) Trial (28, 52) excluded all patients with head and neck location but showed a significant correlation between trunk location and lower DFS and OS.

The utilization of SLNB varied among the studies in this review. In three studies, SLNB was fully implemented (49, 55, 57), while in four studies, it was partially implemented (12, 28, 29, 52). In five studies, SLNB information was not provided, or it was not performed (25-27, 31, 47, 48, 50, 51, 58, 62). In two trials, the Swedish MSG Trial and Intergroup MSG Trial (25, 26, 47, 50, 51), the absence of SLNB data can be attributed to the data collection period predating the widespread adoption of SLNB (69). Only two trials examined the impact of a positive SLNB on recurrence; Doepker et al. (29) and Dalal et al. (55), while von Schuckmann et al. (62) examined the impact on DFS, all of which showed a significant correlation (see Table 5). The rate of SLNB execution varied among the studies; in Dalal et al.'s study (55), SLNB was performed in 100% of cases, in Doepker et al.'s research (29), SLNB was not conducted in 100 out of 965 patients. In von Schuckmann et al.'s study (62), SLNB was performed in 39.9% of cases. This variation in SLNB execution rates affects the results and their generalizability in this review (43).

Table 5. Significance of clinicopathological characteristics in included studies.

	Swedish MSG Trial			**Swedish/ Danish MSG Trial**		**Intergroup Trial**	**European/ French Trial**				**UK MSG Trial**	
	Cohn-Cedermark (2000) (25), Ringborg (1996) (51)	Dalal (2007) (55)	Doepker (2016) (29)	Gillgren (2011) (28), Utjés (2019) (52)	Hunger (2015) (49)	Balch (1993, 2001) (26, 47), Karakousis (1996) (50)	Khayat (2003) (27)	Lee (2017) (57)	Leen-eman (2019) (58)	Rockberg (2016) (12)	Thomas (2004) (31), Hayes (2016) (48)	von Schuckmann (2019) (62)
Excision margin utilized cm:	2 / 5	WLE	1 / 2	2 / 4	1 / 2	2 / 4	2 / 5	NA	NA	NA	1 / 3	WLE
Age median (mean)	51.5	56	64, Yes^{OS}	59, Yes^{OS} No^{DFS}	61.84	47.7 (48.9)	(44), No$^{OS/DFS}$	62	55.5	62.9 (61.3) Yes$^{OS/LR/DR}$	(57.5), Yes^{OS}, No^{DFS}	(62.2), No^{DFS}
Male gender	-	-	Yes^{OS}	Yes$^{OS/DFS}$	-	-	Yes$^{OS/LR/DR}$	-	-	Yes$^{LR/DR}$	Yes$^{OS/DFS/LR}$	No^{DFS}
Tumor thickness	-	Yes$^{LR/DR}$	Yes^{LR}	Yes$^{OS/DFS}$	-	Yes$^{OS/LR}$	Yes$^{OS/LR/DR}$	-	-	-	Yes$^{OS/DFS/LR}$	Yes^{DFS}
Stage	-	Yes^{DFS}	-	-	-	Yes$^{OS/LR}$	-	-	-	Yes$^{OS/DFS/LR/DR}$	Yes$^{OS/DFS/LR}$	Yes^{DFS}
Ulceration	-	Yes$^{LR/DR}$	No^{LR}, Yes^{OS}	Yes$^{OS/DFS}$	-	Yes$^{OS/LR/DR}$	-	-	-	-	Yes$^{OS/DFS/LR}$	Yes$^{OS/DFS}$
Margin of excision (comparing two sets of excision margins, as specified in each study)	No OS/DFS/LR/DR	-	No$^{LR/DR}$ Yes^{OS}	No$^{OS/DFS/LR/DR}$	No$^{OS/DFS/LR/DR}$	No OS/DFS/LR/DR	No$^{OS/DFS/LR}$	-	-	-	Yes$^{DFS/LR}$ No^{OS}	-
Site of tumor	-	-	Yes^{LR}	Yes$^{OS/DFS}$	-	Yes$^{OS/LR}$	No$^{OS/DFS}$	-	-	-	Yes^{OS}, No$^{DFS/LR}$	Yes^{DFS}
Trunk	-	-	-	Yes$^{OS/DFS}$	-	No^{LR}	-	-	-	-	-	-
Lower extremity	-	-	-	No$^{OS/DFS}$	-	No^{LR}	-	-	-	-	-	-
Upper extremity	-	-	-	No$^{OS/DFS}$	-	No^{LR}	-	-	-	-	-	No^{DFS}
Head-neck	-	-	Yes^{LR}	-	-	Yes$^{OS/LR}$	-	-	-	-	-	Yes^{DFS}
Site of recurrence	-	Yes^{OS}	-	-	-	-	No$^{OS/DFS}$	-	-	-	-	-
Histogenetic type	-	-	-	-	-	-	No$^{OS/DFS}$	-	-	-	-	Yes^{DFS}
Clark level of invasion	-	-	-	-	-	Yes$^{OS/LR/DR}$	-	-	-	-	-	-
Median time to recurrence	-	-	-	-	-	-	-	-	-	-	Yes^{LR}	Yes^{DFS}
Sentinel lymph node pathology	-	Yes$^{LR/DR}$	Yes^{LR}	-	-	-	-	-	-	-	-	Yes^{DFS}
Mitotic rate	-	-	-	-	-	-	-	-	-	-	-	Yes^{DFS}

Yes=p<.05. No=p>.05. - =Not analyzed.
OS = Overall Survival, DFS = Disease Free Survival, LR = All local, regional or lymph node recurrence, DR = Distant recurrence. WLE = Wide Local Excision, not defined further, NA = Not applicable.
Studies with several articles, where findings have changed or differed, are mainly presented by the most recent article.

Discussion

This systematic review and meta-analysis compiles data from twelve studies on melanomas stage I and II across twelve Western countries. Apart from differences in recurrence and survival rates among countries, divergencies emerge in terms of patient inclusion criteria, sample sizes, reported measurements, screening methods, treatment given, and follow-up duration. The identified studies provide an informative general overview of melanoma stage-specific outcomes in Western countries, as well as evident research gaps.

Recurrence and survival rates in Western Countries

The subgroup meta-analysis of various recurrences was executed to address heterogeneity. In the case of investigating [1] data collection years new/old (cutoff at the year 2000), and [3] quality assessments made (moderate/high quality, see table 2), none of the variables were found to be significant in terms of differences between the groups ($p > 0.05$). These non-significant variables are unlikely to explain the observed study result variations. Due to the consistent results, these forest plots are not included in the appendices. In the examination of [2] median follow-up duration (± 5 years), disparities emerged, with statistically significant group differences ($p = 0.00$) or approaching significance ($p = 0.06/0.09$) observed in relation to total any recurrence and regional lymph node recurrence, for both stage I and II (see Additional file 4.3). These findings underscore the important role that follow-up duration plays in influencing the outcomes of total recurrence and regional lymph node recurrence in both stages. It is our assessment that while older studies may have suboptimal data collection timelines, they are valuable by offering long-term follow-up. While we did not find significant results regarding heterogeneity for local or distant recurrence in this analysis, it is important to interpret these findings in the context of the study limitations and the need for further research to better understand these aspects of melanoma recurrence.

The pooled OS based on weighted means in stage I (Fig. 2b), shows a relatively stable decrease over time, with a similar trend in the pooled OS based on unweighted means. These findings suggest that survival rates are relatively high in the earlier years of stage I, but gradually decrease with extended follow-up. The pooled OS based on weighted means in stage II (Fig. 4b) show a more pronounced and rapid decline in survival, with the most significant drop occurring between the 1-year and 5-year marks. A tendency for mortality rates to level off is observed in stage II over time, as also reflected in the pooled OS based on unweighted means. These findings align with a recent large German study involving 17,544 patients diagnosed with stage I and II melanoma from 2000 to 2015, where a substantial

proportion of recurrences and deaths occur more than 5 years after initial surgery. In this German study, stage I mortality is almost equally distributed in the first and second 5-year periods, whereas in stage II, more patients die in the first 5-year period, with still a large proportion dying in the second 5-year period (70), all consistent with our study. This may be influenced by multiple factors such as disease progression, treatment effectiveness, patient characteristics, and background mortality. Results for pooled OS are also presented numerically in Table 4. This data aligns with the knowledge of the close association between ulceration in melanoma and increased tumor thickness (21, 22). The pronounced decline in survival within stage II is corroborated by the AJCC classification (8), wherein ulcerations signifies a higher stage and a more unfavorable tumor biology (19, 20), resulting in diminished survival. Stage II studies with complete data on 2-year, 5-year, and 10-year OS (refer to Table 4) (e.g., Leeneman et al. (58), Hayes et al. (48), and Utjés et al. (52)), demonstrate similar OS trends. This suggests a consistent pattern of OS over time for stage II melanoma patients, even with varying median follow-up durations of 5.4, 8.8, and 19.6 years, respectively.

In Figs. 3b and 5b we observe a more favorable DFS trend for stage I compared to stage II melanomas, indicating a better prognosis for early-stage melanoma. The pooled DFS based on weighted means in both stage I and II follows a somewhat similar pattern as for OS. In stage I, it shows a consistent gradual percentage point decline, with the decline almost evenly distributed across the first and second 5-year periods (Fig. 3b), with a further leveling off after 10 years. At 10 years, the values decrease to approximately 68%, remaining relatively high compared to the initial point. In contrast, pooled DFS based on weighted means in stage II experiences a more pronounced drop within the initial 5-year period (Fig. 5b), suggesting a shorter time to, and higher risk of, disease recurrence. At 10 years, the values decrease to approximately 48%, indicating a substantial decrease in DFS over the long term. A similar trend in seen in the pooled DFS based on unweighted means in both stages. The incidence of pooled DFS based on weighted means ceased after 8 years in stage II, with no new cases occurring for those studies with estimates up to 10 years (28, 55). This suggests that recurrence of melanoma stabilizes at a relatively lower level after 8 years in stage II, while stage I showed a further 10% decline in DFS two years later (Fig. 3b). This is supported by evidence from another study included in this review, albeit not factored into this analysis due to its inclusion of combined stages Ib and II, the Intergroup MSG Trial (26). This trial reported that all local recurrences occurred within 8 years, making it unlikely that recurrence

rates would significantly change with a longer follow-up period, as the median follow-up period was already 10 years. Detailed numerical data on this study are provided in Table 4.

The pooled effect estimates from the meta-analyses, along with 95% confidence intervals and heterogeneity in the recurrence subgroups, are presented in Table 4 and Additional files 4.0 and 4.1. In stage I, three studies reported on distant recurrence (25, 27, 55), showing a pooled effect of 5.2 (4.4-6.4, I^2=4.94%) in random-effects model. The fixed-effect model showed consistent results with I^2=0%, indicating homogeneity and agreement among the studies (66), supporting the observation that definitions and measurements for distant recurrence were relatively consistent among the included studies, particularly in stage I. In contrast, the heterogeneity observed in distant recurrence in stage II is substantial, with a pooled effect of 13.1 (9.0-17.4, I^2 = 93.49%). One possible explanation for this discrepancy could be that Table 4 clearly indicates that stage I melanomas are less prone to progress to stage III or IV, compared to stage II melanomas, naturally encompassing patients with more advanced and varied tumor biology (20). Moreover, as summarized in Table 5, SLNB-positive patients tend to experience earlier and more frequent recurrences compared to SLNB-negative patients (29, 55, 62). The observed heterogeneity, in distant recurrence stage II, may be attributed to the inclusion of SLNB in only three (49, 55, 57) out of six studies analyzed, leading to potential variations in reporting. On that note, it is anticipated that all future research and treatment strategies for stage I and II melanomas will encompass the utilization of SLNB when indicated, aligning with the latest guidelines (8). The pursuit of earlier and more precise diagnoses is a shared goal, benefiting both patients and the healthcare system.

Local recurrence exhibits a pooled effect, along with 95% confidence intervals and heterogeneity, from the meta-analysis of 0.6 (0.2-1.4, I^2=61.13%) (I^2=58.27% fixed-effect model) in stage I and 2.4 (1.6-3.6, I^2=69.19%) (I^2=67.19% fixed-effect model) in stage II, indicating a moderate level of consistency (Additional file 4.0 and 4.1). While all the included studies analyze local recurrence, diverse definitions for local recurrence have been noted by the authors, and Gillgren and colleagues (28), as a potential source of heterogeneity in the results. For instance, the Intergroup Trial (26) and Khayat et al. (27) define local recurrence as occurring within 2 cm of the scar, whereas von Schuckmann et al. (62) considers it to be within 5 cm of the scar. In contrast, the Swedish/Danish MSG Trial (25) classifies recurrences beyond the scar as regional skin metastasis. This variance in local recurrence definitions may lead to differences in the biological characteristics of the reported cases, potentially explaining the observed heterogeneity.

Furthermore, recurrences falling between local and distant recurrence are all exhibiting a widespread pooled effect and confidence intervals (see Table 4), and low heterogeneity (I^2 = >97.16%) (see Additional file 4.0 and 4.1), and it is natural to assume that differences in terminology and definitions of the recurrence are factors contributing to this pattern.

The patients included in this study were diagnosed between 1981 and 2014, predating the introduction of SLNB in the early 1990s (69). Now, SLNB plays a crucial role in melanoma staging, routinely used worldwide, especially in the United States, Australia, and Western Europe (71-73), and its critical impact has been well-established (74). A Swedish systematic review from 2016 (75) highlights a phenomenon known as the “Will Rogers phenomenon”. The introduction of SLNB may have led to stage migration in Western countries where it is practiced, potentially resulting in some patients being reclassified from stages I and II to stage III. Consequently, the survival rates in stages I and II might appear improved, as patients with microscopically positive lymph nodes and poorer prognoses are correctly categorized as stage III. Simultaneously, stage III may now include patients with relatively better prognoses (microscopically positive lymph nodes), potentially resulting in an overall enhanced prognosis for stage III melanoma. Examining Figs. 4a and 5a, which depict DFS and OS in stage II based on the included studies (also summarized in Table 4), Hunger et al. (49) stands out with higher OS and DFS during the first 7 years. This divergence of higher DFS and OS could be attributed to the fact that Hunger et al.'s study is unique in its utilization of SLNB for stage II, possibly exemplifying the phenomenon of stage migration and its impact on higher DFS and OS rates within the study's stage II population.

Predictors of recurrence and survival

Regarding relevant clinicopathological characteristics reported (Table 5), strong associations are observed between male gender and both DFS and OS, and these findings align with previous research conducted by Dong et al. (19) and Bay et al. (14). Joosse et al. (76) reports that women exhibit an independent relative 30% advantage in all aspects of the progression of stage I and II melanoma. This advantage is likely influenced by underlying biological sex differences and is partly associated with the earlier detection of melanoma in women. This trend is further supported by a study conducted by Eriksson et al. (77). Men have the greatest need for increased knowledge and awareness, according to a Norwegian study by Robsham et al. (78), both in terms of taking preventive care of their skin and seeking timely medical assistance in case of an abnormal mole.

All relevant studies (12, 26-29, 31, 47, 48, 50, 52, 55, 62) demonstrate a consistent increase in mortality and recurrence rates as the melanoma advances. Ulceration is a recognized prognostic factor linked to reduced DFS and OS, with some studies suggesting even minimal ulceration can affect melanoma survival (22). The strong association between ulceration and greater tumor thickness is well-established (21). Ulceration is a key element in the AJCC staging system for cutaneous melanoma (8), and this correlation has been upheld by all studies in this review that examined it (26, 28, 29, 31, 47, 48, 50, 52, 55, 62). Notably, Doepker et al. (29) was the only study not to find a significant connection between ulceration and local recurrence, possibly due to its exclusive focus on stage IB and IIA melanomas with a thickness range of 1.01-2.0 mm, thus excluding the extreme thicknesses of stage II, 2.0->4.0 mm. This specific focus may not have provided enough variability in tumor thickness to detect a significant influence of ulceration. Two other studies in this review examined melanomas <2.0 mm, but neither reported on the correlation between ulceration and recurrence (25, 27, 51).

The WHO melanoma program (79, 80) conducted the initial randomized trial investigating excision margins. These findings align with contemporary practice (9), demonstrating the safety of a 1 cm excision margin in primary melanomas <2.0 mm. This conclusion is further substantiated by the evidence presented in this review, including studies by Khayat et al. (27) and The Swedish Melanoma Study Group trial (25, 51).

In the long-term follow-up conducted by Hayes et al. (48) in the UK MSG Trial (31), and in Doepker et al.'s (29) study, it's suggested that a 1 cm excision margin may not be sufficient for advanced ≥2.0 mm melanomas, impacting DFS and OS. This is supported by Sladden and colleagues' Cochrane review (9) and most national protocols (32-35). However, conflicting results are seen, as the Australian Cancer Network (35) recommends a 1-2 cm margin for ≥2.0 mm melanomas, and Hunger et al. (49) found no significant differences in DFS or OS between 1 cm and 2 cm margins. In other words, the findings are conflicting. The ongoing MelMART trial may provide a more definitive answer; a multinational, prospective RCT assessing the safety of 1- versus 2 cm margins for ≥1 mm thick melanomas, all of which are undergoing SLNB, set to conclude by December 2029 and involve approximately 10,000 patients (81-83). A 2018 Cochrane review update also suggests that with more effective systemic adjuvant therapies, wider margins may become unnecessary in the future (84), potentially settling the long-standing debate on excision margins.

Several trials, as presented in Table 5 (26, 29, 47, 50, 62), suggest that melanoma location on the head and neck leads to a poorer prognosis compared to the trunk and extremities, consistent with AJCC guidelines (8, 10) and prior research (85-87). The Intergroup Trial's data (26, 47, 50), after a 10-year follow-up, reveals higher local recurrence rates and worsened OS for melanomas located on the head, neck, or distal extremities (highlighted in Table 4). In contrast, a Norwegian study from 2016 (88) challenges this observation, as it did not find location to be a significant prognostic factor for head and neck melanomas. Despite Norway having one of the highest melanoma incidence rates globally (5), it is conceivable that sunbathing habits and a potential lack of awareness among Norwegians may still predispose them to melanoma on other parts of the body. Indeed, a 2013 Norwegian population study (89) indicates a shift towards trunk melanomas. Increased melanoma incidence among white populations living near the equator and regions with high solar radiation, particularly in people of European descent (7), suggests that UV radiation exposure plays a more substantial role in head and neck melanomas, especially in warmer Southern countries. The Nordic study, the Swedish/Danish MSG Trial by Gillgren et al. (28) and Utjés et al. (52), supports this idea by revealing a connection between trunk location and lower DFS and OS in participants from Sweden, Denmark, Estonia, and Norway. Nonetheless, this study does not examine correlations with head and neck locations.

Limitations, strengths, and future direction

One limitation of the evidence included were that the meta-analysis confirmed prior assumptions of inconsistent terminology and definitions for recurrence, challenging comparability and introducing challenges related to homogeneity. Various recurrence groupings were employed across studies contributing to confusion, as described in Table 3; local, regional, regional skin, regional node, locoregional, in-transit, combined local/in-transit, combined regional node/in-transit, intralymphatic, nodal, combined regional skin and node, distant and systemic recurrence. This variation in outcome definitions hindered the seamless grouping of results and can lead to confusion and inconsistency when attempting to comprehend the specific events being reported during the comparison and summarization of results. Similarly, the definitions of OS and DFS in the articles were at times unclear. Additional complexities arose from variations in median follow-up duration, tumor thickness categorization, diagnostic tools, and melanoma site. It is imperative to acknowledge and account for these diversities when interpreting the results and drawing meaningful conclusions from the body of evidence (43). To address these complexities, standardized

outcome reporting is essential in future research to enhance comparability and understanding. Future research should aim to further explore and understand the sources of heterogeneity and identify potential strategies to mitigate its impact on meta-analyses in this field.

A second limitation in this review, is the use of a single-author screening process. This is a methodological weakness, as it may introduce bias, inconsistencies, and errors in the inclusion process (43). Multiple researchers should be involved to enhance reliability and accountability[1].

The inclusion criterion regarding "excision margins" (criterion #2) was adjusted to accommodate studies reporting only Wide Local Excision (WLE) without specified margins (see specific studies in Table 3), ensuring vital data inclusion, even at the expense of some review reliability. The alternative, stricter criteria, would risk lacking validity due to limited data.

The review's strengths lie in its comprehensive search, examining numerous factors related to recurrence and survival, and the application of various analytical methods for data analysis. Despite a lack of uncertainty information in more than two of the original articles included, hindering direct integration into meta-analyses, we opted for the inverse variance methodology involving the pooling of studies and estimation of confidence intervals (CIs). The methods employed are rooted in models suitable for binomial distributions. This distribution is obtained by setting recurrence equal to the number of individuals with recurrence divided by the number of individuals who were in the study from the start. We also assume a binomial distribution for our pooled estimates for DFS and OS.

Notably, for recurrence estimates, inherent uncertainty arises due to the unavailability of data on study dropout (non-responsive participants, relocation, etc.). Similar to the original articles, we calculate the recurrence proportion based on the initial study cohort, potentially lowering the recurrence rates below their actual values. This discrepancy introduces a deviation in our pooled estimates derived from these studies. However, this issue does not seem to affect DFS and OS outcomes, where we incorporate dropouts through censoring in Kaplan-Meier analyses, making the methods more suitable for these measures.

A strength therefore lies in the pooled estimates for DFS and OS in Figs. 2b-5b, where we combine all the graphs in the form of unweighted and weighted means, closely aligning with the results of the meta-analyses using random-effects and fixed-effects methods, respectively (see Additional file 8.0 for a comparison of pooling methods).

By acknowledging the strong correlation between tumor thickness and ulceration, healthcare providers and policymakers can make more informed decisions about risk assessment and early intervention strategies for melanoma. The lower survival rates observed in men, especially high in age, underline the importance of targeted awareness campaigns and early detection strategies. Policymakers should consider allocating resources for public health campaigns tailored to men, highlighting the importance of early intervention and the role of healthcare providers in melanoma detection. Encouraging older men to be proactive about regular skin checks and promptly seeking medical attention for abnormal moles can potentially lead to earlier diagnoses and improved outcomes.

Future research should look deeper into gender-based disparities in melanoma survival, exploring social, cultural, and behavioral factors influencing men's engagement with melanoma screening and healthcare-seeking behaviors. Additionally, studies on interventions for early detection among high-risk populations, especially older men, can mitigate the disease's impact.

Conclusion

This systematic review shows a consistent increase in mortality and recurrence rates as the melanoma advances, with stage I mortality and recurrence showing nearly equal distribution across the initial and subsequent 5-year periods, while in stage II, a greater number of patients experience death and recurrence in the initial 5-year period, emphasizing a significant correlation between ulceration and advanced stage. Factors like follow-up duration significantly influenced total recurrence and regional lymph node recurrence in both stages. Clinicopathological characteristics, including age, gender, tumor thickness, ulceration presence, melanoma location, and SLNB, exhibited statistically significant associations with recurrence and survival. The review highlights the challenges of comparing studies between countries and underscored the need for international standardized reporting using a joint staging system.

Other information

This systematic review was conducted by master student and author 1 (GNS), at the request of authors 2 and 3 (LTN and PJ). This master thesis is a contribution to a larger research project aimed at examining cost-benefit in regards of different preventive measures targeting the general population in Norway to reduce the incidence and mortality of melanoma.

Author 1 (GNS) is responsible for composing all sections of the written article and the tables presented. Data collection and the analysis of findings are verified by authors 2 and 3 (LTN/PJ). The meta-analysis and graphs presented are a joint effort collaboration between authors 1 and 3 (GNS/PJ). Authors 2 and 3 (LTN/PJ) contributed to the conceptualization of the study design and provided continuous feedback on content and tables. A protocol was prepared by author 1 (GNS) in the form of a project description for the master's thesis project. The study was not registered[1]. Confirmation that no recent similar review existed, or was in development, was made prior to the systematic search by author 2 (LTN) and 3 (PJ), to prevent redundancy.

The authors have no funding to disclose for this review. The authors declare that they have no competing interests. Data used in this review were collected from the research articles listed in Table 3. Other datasets on forest plots and graphs used and/or analyzed during the current study are available from the corresponding author on reasonable request.

[1]Kommentar fra hovedveileder (PJ) til sensorene: Studenten er klar over at PRISMA legger opp til at det er minst to personer som skal gjøre denne delen av arbeidet parallelt, for deretter å vurdere om de kommer fram til det samme utvalget av artikler for den videre prosessen, og at det ved uenighet drøftes med en tredjeperson. I utgangspunktet ble det til denne masteroppgaven søkt etter to studenter. Det meldte seg imidlertid kun en student (GNS). Det er viktig å understreke at det er hovedveileder (PJ) som har ansvaret for beslutningen om at masterprosjektet gjennomføres med denne ene studenten. Dette innebar videre at det ble bare en person (GNS) som gjorde denne første utvelgelsen av referanser/artikler. Dersom studenten og veilederne, etter sensurering, ønsker å jobbe videre med artikkelen med mål om å publisere denne i f.eks. BMC Cancer, vil de to veilederne foreta en parallell-gjennomgang av hver sin halvpart av funnene ved litteratursøket. Ved diskrepans mellom seleksjonen foretatt av studenten og veilederne, vil dette drøftes med den tredje i forfattergruppen. Eventuelle endringer i hvilke artikler som blir valgt ut vil så innarbeides i artikkelen før publikasjon.

Videre var det også hovedveileder (PJ) sine vurderinger som lå bak at studien ikke ble registrert. Ved tidligere publisering av meta-analyse i BMC Palliativ Care har det ikke vært oppmerksomhet på dette, og mer generelt at systematiske oppsummeringer som ikke oppsummerer effekter av intervensjoner i liten grad blir registrert i forkant (se f.eks. Migliavaca et.al. (2020)). Hovedveileder (PJ) ser i ettertid at det er gode grunner for å foreta slike registreringer i forkant av arbeidet med slike analyser, og det bør være en standard.
Referanse for kommentaren fra PJ: Borges Migliavaca, C., Stein, C., Colpani, V. et al. *How are systematic reviews of prevalence conducted? A methodological study*. BMC Medical Research Methodology. (2020) 20:96. https://doi.org/10.1186/s12874-020-00975-3

Det ble undersøkt, og godkjent, av hovedveileder (PJ) at masterstudent (GNS) kunne skrive denne systematiske reviewen med meta-analyse som sin masteroppgave ved Masterstudium i helsevitenskap, spesialisering i Kreftsykepleie, uten sykepleiefaglig fokus i artikkelen. Tematikken anses som relevant for valgt masterstudium.

Additional file 1.0: PRISMA 2020 Checklist for abstracts
Additional file 1.1: PRISMA 2020 Checklist for systematic reviews
Additional file 2.0: Systematic search details
Additional file 3.0: AJCC Eighth Edition Melanoma Staging System
Additional file 4.0: Forest plots from random-effects models: recurrence
Additional file 4.1: Forest plots from-effects models: recurrence
Additional file 4.2: Forest plots from random- and fixed-effects models: DFS and OS
Additional file 4.3: Forest plots from random-effects models: recurrence and follow-up
Additional file 5.0: Example of spreadsheet for transformations
Additional file 6.0: Example of pooled curves unsuitable as OS or DFS survival curves
Additional file 7.0: Excluded studies after quality assessments
Additional file 8.0: Comparison of different pooling methods for DFS and OS

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Appendices

Additional file 1.0: PRISMA 2020 Checklist for abstracts

Selected scientific journal: BMC Cancer. **The article's author guidelines refer to the application of PRISMA 2020**: https://bmccancer.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Additional file 1.1: PRISMA 2020 Checklist

Selected scientific journal: BMC Cancer. **The article's author guidelines refer to the application of PRISMA 2020**: https://bmccancer.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Front page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7-9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6-7
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Page 6-7 Add. file 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 8-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 8-9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 8-9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7-8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 9-12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 9-12
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 9-12
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 9-12
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 9-12
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 11-12
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 9-12
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 9-12

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig. 1, page 13-14
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 14 Add. file 7.0
Study characteristics	17	Cite each included study and present its characteristics.	Table 3, page 15-16
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 2, page 14
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 4 & 5, page 23, and 26
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 3, page 15-16
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Fig. 2-5, table 4, page 19-23. Add. file 4.0-4.3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 17-18 + 24-25
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 17-18
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 17-18 + 24-25
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 17-18 + 24-25. Table 4, page 23
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 27-32
	23b	Discuss any limitations of the evidence included in the review.	Page 32-33
	23c	Discuss any limitations of the review processes used.	Page 33
	23d	Discuss implications of the results for practice, policy, and future research.	Page 33-34
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 35
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 35
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 33
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 35
Competing interests	26	Declare any competing interests of review authors.	Page 35
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 35

Additional file 2.0: Systematic search details

MEDLINE (Ovid) search #1
Initial search date: 24th of May 2022

1. Melanoma/
2. "melanoma*".ab,ti.
3. 1 or 2
4. "surgical excision*".ab,ti.
5. "Margins of Excision"/
6. "excision margin*".ab,ti.
7. (breslow* and (depth or thickness)).ab,ti.
8. surgical technique*.mp.
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9
11. Neoplasm Staging/
12. ((tumor or cancer or TNM) and staging).ab,ti.
13. TNM classification*.mp.
14. 11 or 12 or 13
15. 10 and 14
16. Recurrence/ or Neoplasm Recurrence, Local/
17. recurrence rate*.ab,ti.
18. Recrudescence*.ab,ti.
19. Recurrence*.ab,ti.
20. Relapse*.ab,ti.
21. 16 or 17 or 18 or 19 or 20
22. 15 and 21

Articles retrieved in MEDLINE search #1: 266.

Articles included based on title screening in search #1: 21.

MEDLINE (Ovid) search #2

Initial search date: 24th of May 2022

The search has focused on TNM staging, melanoma, and recurrence, excluding surgical techniques and the 266 articles found in MEDLINE search #1

1 Melanoma/ 93142

2 "melanoma*".ab,hw,kf,ot,sy,ti,fx,nm,ox,px,rx,ui. 149338

3 1 or 2 149338

4 "surgical excision*".ab,hw,kf,ot,sy,ti,fx,nm,ox,px,rx,ui. 24615

5 "excision margin*".ab,hw,kf,ot,sy,ti,fx,nm,ox,px,rx,ui. 668

6 (breslow* and (depth or thickness)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 2218

7 surgical technique*.mp. 68991

8 4 or 5 or 6 or 7 95887

9 3 and 8 3732

10 Neoplasm Staging/ 189200

11 ((tumor or cancer or TNM) and staging).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 184956

12 TNM classification*.mp. 3992

13 10 or 11 or 12 221574

14 9 and 13 817

15 Recurrence/ or Neoplasm Recurrence, Local/ 330538

16 recurrence rate*.mp. 44180

17 Recrudescence*.mp. 3132

18 Recurrence*.mp. 565397

19 Relapse*.mp. 183477

20 15 or 16 or 17 or 18 or 19 687120

21 14 and 20 266 (= search #1)

22 3 and 20 10376

23 13 and 22 1753

24 23 not 21 1487 (= search #2)

Articles retrieved in MEDLINE search #2: 1487.

Articles included based on title screening in search #2: 89.

(Articles retrieved in MEDLINE search #1 and #2 in total: 1753.)

Embase (Ovid) search #1
Initial search date: 9th of June 2022

1 melanoma/ 147857

2 melanoma*.ti,ab. 180186

3 1 or 2 216847

4 "surgical excision*".ti,ab. 32525

5 "excision margin*".ti,ab. 1136

6 (breslow* and (depth or thickness)).ti,ab. 3565

7 surgical technique*.ti,ab. 89735

8 excision/ 57369

9 4 or 5 or 6 or 7 or 8 172286

10 cancer staging/ 403921

11 ((tumor or cancer or TNM) and staging).ti,ab. 92895

12 TNM classification*.ti,ab. 5990

13 recurrent disease/ 199135

14 cancer recurrence/ 238095

15 recurrence rate*.ti,ab. 68066

16 Recrudescence*.ti,ab. 3738

17 Recurrence*.ti,ab. 541738

18 relapse*.ti,ab. 321861

19 10 or 11 or 12 442660

20 13 or 14 or 15 or 16 or 17 or 18 1006259

21 3 and 9 and 19 and 20

Articles retrieved in Embase search #1: 506.

Articles included based on title screening in search #1: 53.

Embase (Ovid) search #2
Initial search date: 9th of June 2022

The search has excluded TNM staging, and the 506 articles found in Embase search #1

1 melanoma/ 147857

2 melanoma*.ti,ab. 180186

3 1 or 2 216847

4 "surgical excision*".ti,ab. 32525

5 "excision margin*".ti,ab. 1136

6 (breslow* and (depth or thickness)).ti,ab. 3565

7 surgical technique*.ti,ab. 89735

8 excision/ 57369

9 4 or 5 or 6 or 7 or 8 172286

10 cancer staging/ 403921

11 ((tumor or cancer or TNM) and staging).ti,ab. 92895

12 TNM classification*.ti,ab. 5990

13 recurrent disease/ 199135

14 cancer recurrence/ 238095

15 recurrence rate*.ti,ab. 68066

16 Recrudescence*.ti,ab. 3738

17 Recurrence*.ti,ab. 541738

18 relapse*.ti,ab. 321861

19 10 or 11 or 12 442660

20 13 or 14 or 15 or 16 or 17 or 18 1006259

21 3 and 9 and 19 and 20506

22 3 and 9 and 202097

23 22 not 21 1591

Articles retrieved in Embase search #2: 1591.

Articles included based on title screening in search #2: 59.

(Articles retrieved in Embase search #1 and #2 in total: 2097.)

CINAHL (EBSCO) search #1
Initial search date: 9th of June 2022

S23	S3 AND S9 AND S19	101 = research only
S22	S3 AND S9 AND S19	171 = staging excluded
S21	S3 AND S9 AND S13 AND S19	27 = all 4 elements
S20	S3 AND S9 AND S13 AND S19	45
S19	S14 OR S15 OR S16 OR S17 OR S18	137,535
S18	TI Relapse* OR AB Relapse*	35,176
S17	TI Recurrence* OR AB Recurrence*	64,779
S16	TI Recrudescence* OR AB Recrudescence*	225
S15	TI recurrence rate* OR AB recurrence rate*	12,417
S14	(MH "Recurrence") OR (MH "Neoplasm Recurrence, Local")	77,041
S13	S10 OR S11 OR S12	44,576
S12	TI TNM classification* OR AB TNM classification*	608
S11	TI (((tumor or cancer or TNM) and staging)) OR AB (((tumor or cancer or TNM) and staging))	11,154
S10	(MH "Neoplasm Staging")	38,597
S9	S4 OR S5 OR S6 OR S7 OR S8	22,358
S8	TI surgical technique* OR AB surgical technique*	17,131

S7	TI ((breslow* and (depth or thickness))) OR AB ((breslow* and (depth or thickness)))	304
S6	TI excision margin* OR AB excision margin*	694
S5	TI surgical excision* OR AB surgical excision*	4,347
S4	(MH "Surgical Margin")	371
S3	S1 OR S2	21,034
S2	TI melanoma OR AB melanoma	17,679
S1	(MH "Melanoma")	14,752

Articles found in CINAHL search #1: 101.

Articles included based on title screening in search #1: 6.

Fritekst	malignant melanoma malignant melanomas melanoma	Surgical excision excision margin* Breslow's depth Brslow Surgical tegunique	Tumor staging Cancer Staging TNM Staging TNM Classification* TNM Staging System* TNM Classifications	Recurrence rate Recrudescence* Recurrence* Relapse*
Medline (MeSH)	Melanoma	Surgical Oncology? Neoplasms/surgery? "Margins of Excision"	Neoplasm Staging	Recurrence Survival Rate Disease-Free Survival Neoplasm Recurrence, Local Treatment Outcome
Embase (Emtree)	Melanoma	Excision	Cancer Staging	Recurrent disease Cancer recurrence

Additional file 3.0: AJCC Eighth Edition Melanoma Staging System

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite and/or microsatellite metastases	T Category								
			T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
			No evidence of primary tumor	<0.8 mm without ulceration	<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration	>1.0-2.0 mm without ulceration	>1.0-2.0 mm with ulceration	>2.0-4.0 mm without ulceration	>2.0-4.0 mm with ulceration	>4.0 mm without ulceration	>4.0 mm with ulceration
N0	No regional metastases detected	No	-	IA	IA	IB	IIA	IIA	IIB	IIB	IIC
N1a	1 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N1b	1 clinically detected	No	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N1c	No regional lymph node disease	Yes	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2a	2 or 3 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N2b	2 or 3, at least 1 of which was clinically detected	No	IIIC	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2c	1 clinically occult or clinically detected	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
N3a	≥4 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3b	≥4, at least 1 of which was clinically detected, or the presence of any number of matted nodes	No	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3c	≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID

T0 — no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma); **Tis** — melanoma in situ;
Tx — thickness cannot be assessed. (Tis and Tx are not included in the table but are part of the staging system.)
Nx — Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason).
Exception: pathological N category is not required for T1 melanomas, use clinical N information. (If an SLNB was performed, the results can and *should* be used for pathological evaluation.)

AJCC Eighth Edition: T Category, N Category and Pathological Stage Groups for Stages I to III for Cutaneous Melanoma.

Image is taken from: Keung EZ. Key Changes in the AJCC Eighth Edition Melanoma Staging System. 2018 [Available from: https://www.semanticscholar.org/paper/Key-Changes-in-the-AJCC-Eighth-Edition-Melanoma-Keung/fee4a0812e641c6e1719832de8d53292c7ca9764.

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Continued on page 8

M Category	M Criteria	
	Anatomic Site	LDH Level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	
M1a	Distant metastasis to skin, soft tissue including muscles and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

AJCC Eight Edition: Definition of distant metastasis and Pathological Stage Group IV in melanoma.

Image is taken from: Keung EZ. Key Changes in the AJCC Eighth Edition Melanoma Staging System. 2018 [Available from: https://www.semanticscholar.org/paper/Key-Changes-in-the-AJCC-Eighth-Edition-Melanoma-Keung/fee4a0812e641c6e1719832de8d53292c7ca9764.

LDH level (lactate dehydrogenase) is an enzyme blood test that measures the level of damaged or diseased tissues in the body (including red blood cells, skeletal muscles, kidneys, brain, and lungs). Source: University of Rochester Medical Center. Health Encyclopedia [Available from: https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=lactic_acid_dehydrogenase_blood.

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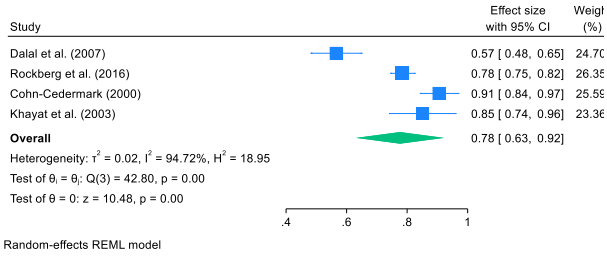
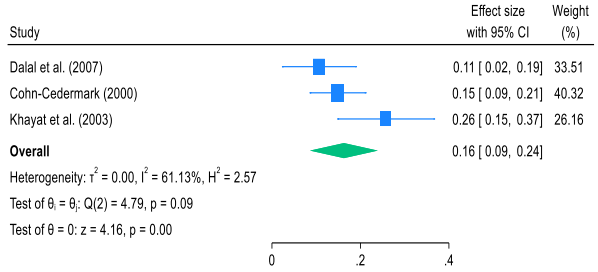
Additional file 4.0: Forest plots from random-effects models: recurrence

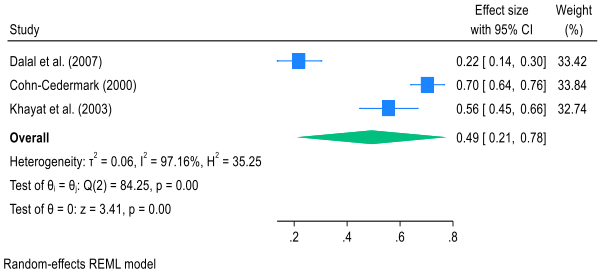
Stage I - Total recurrence:



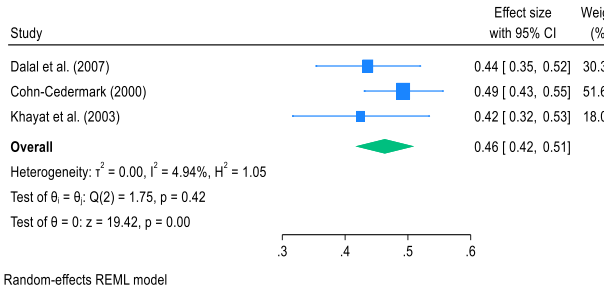
Stage I - Local recurrence



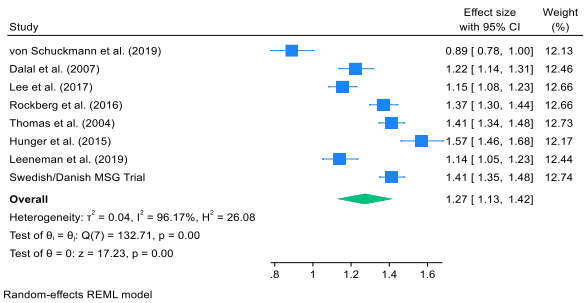
Stage I - Regional lymph node recurrence



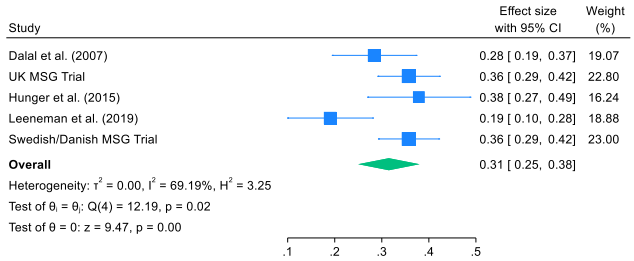
Stage 1 - Distant recurrence



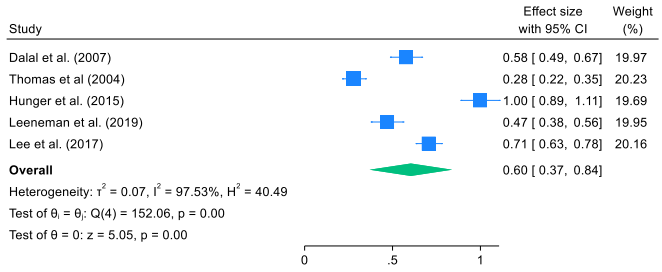
Stage II – Total recurrence:



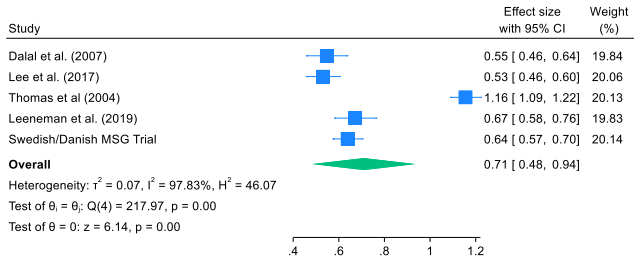
Stage II – Local recurrence



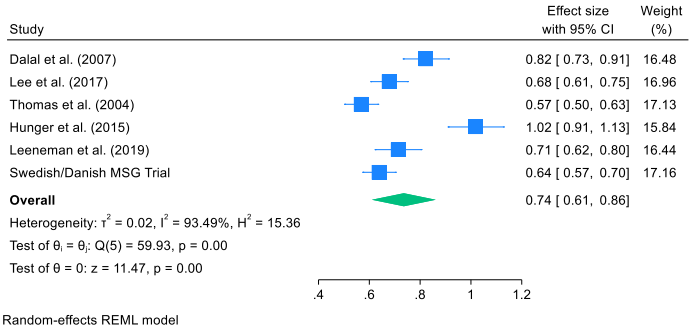
Stage II – In-transit recurrence



Stage II – Regional lymph node recurrence

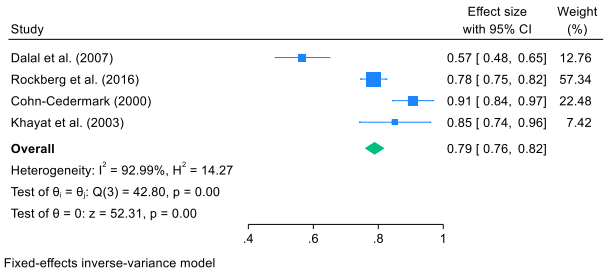


Stage II – Distant recurrence



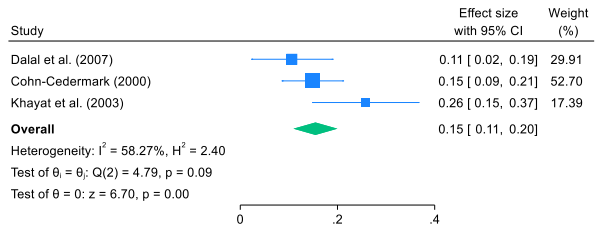
Additional file 4.1: Forest plots from fixed-effects models: recurrence

Stage I - Total recurrence:



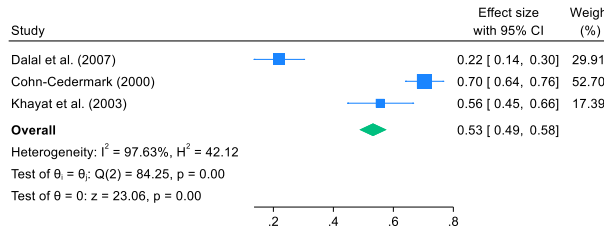
Fixed-effects inverse-variance model

Stage I - Local recurrence



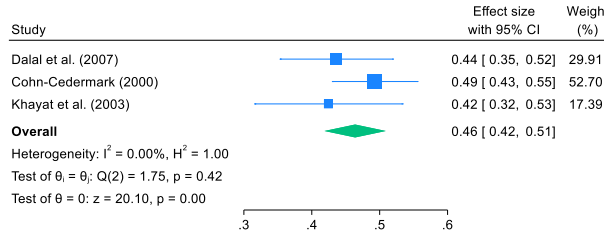
Fixed-effects inverse-variance model

Stage I - Regional lymph node recurrence



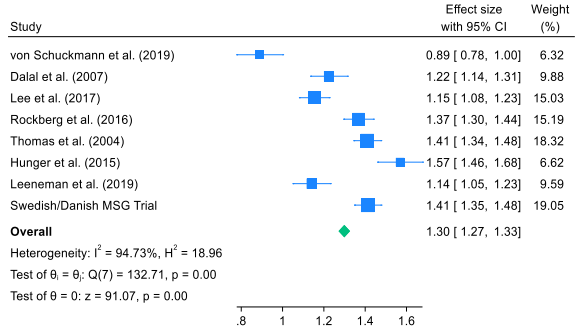
Fixed-effects inverse-variance model

Stage 1 - Distant recurrence



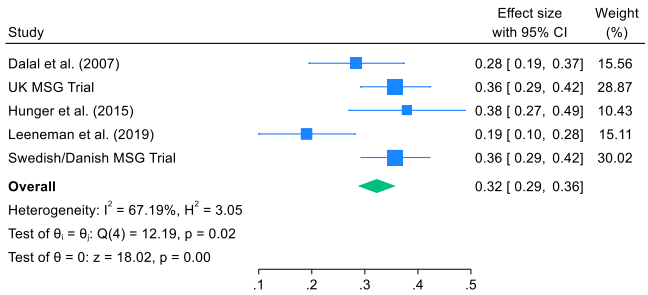
Fixed-effects inverse-variance model

Stage II – Total recurrence:



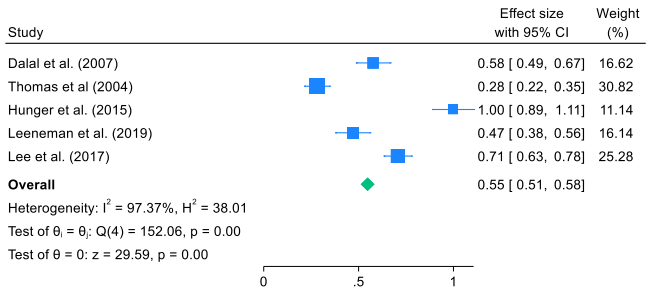
Fixed-effects inverse-variance model

Stage II – Local recurrence



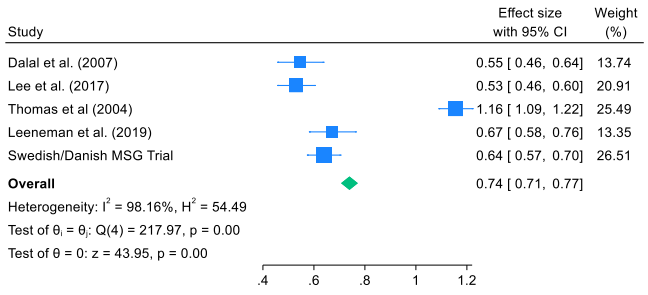
Fixed-effects inverse-variance model

Stage II – In-transit recurrence



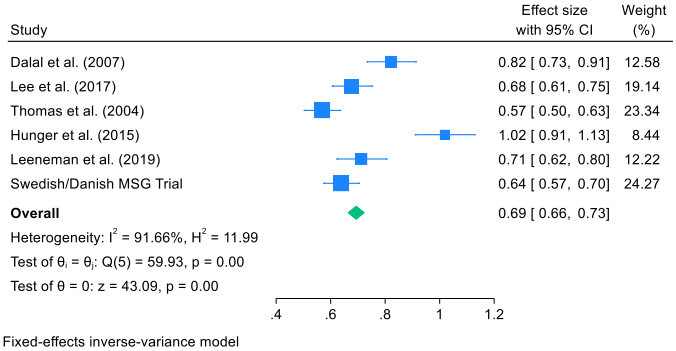
Fixed-effects inverse-variance model

Stage II – Regional lymph node recurrence



Fixed-effects inverse-variance model

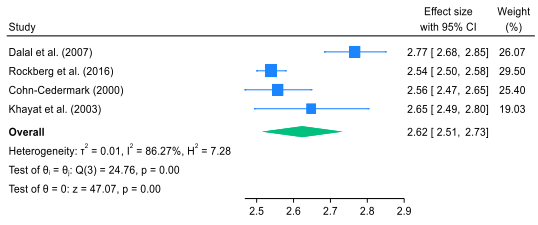
Stage II – Distant recurrence



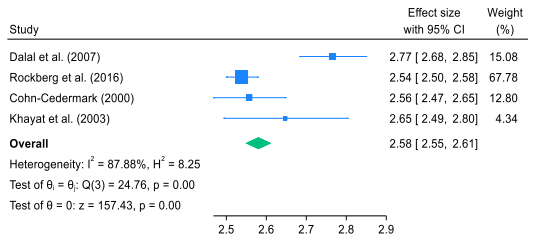
Fixed-effects inverse-variance model

Additional file 4.2: Forest plots from random- and fixed-effects models: DFS and OS

DFS Stage I – 2 years

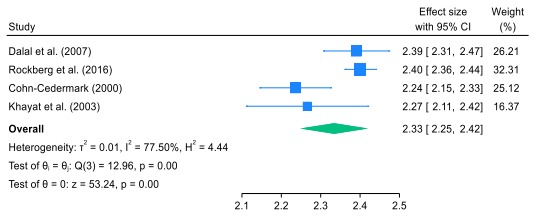


Random-effects REML model

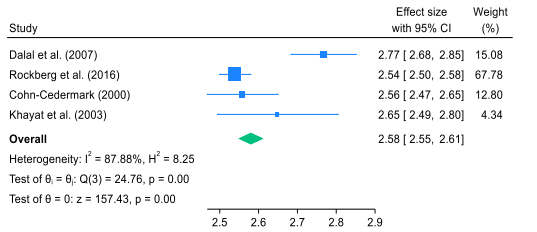


Fixed-effects inverse-variance model

DFS Stage I – 5 years

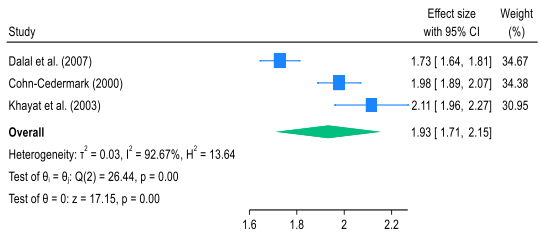


Random-effects REML model

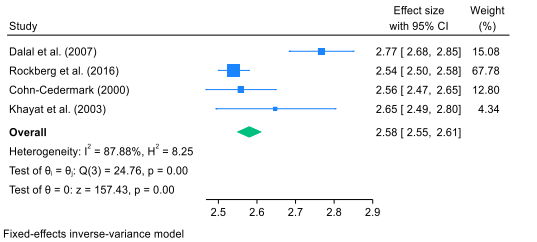


Fixed-effects inverse-variance model

DFS Stage 1 – 10 years

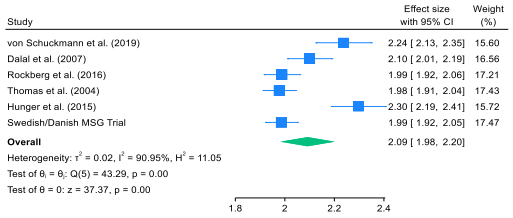


Random-effects REML model

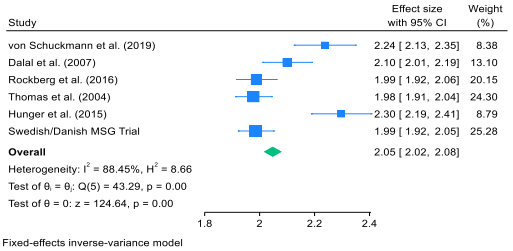


Fixed-effects inverse-variance model

DFS Stage II – 2 years

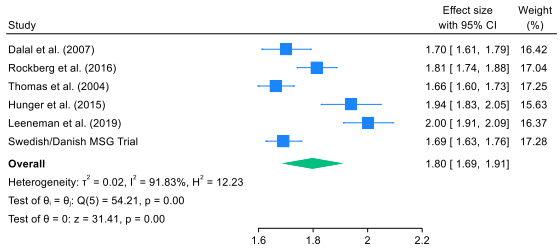


Random-effects REML model

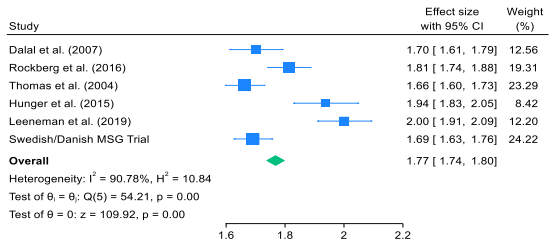


Fixed-effects inverse-variance model

DFS Stage II – 5 years

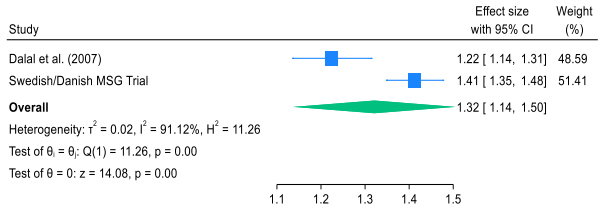


Random-effects REML model

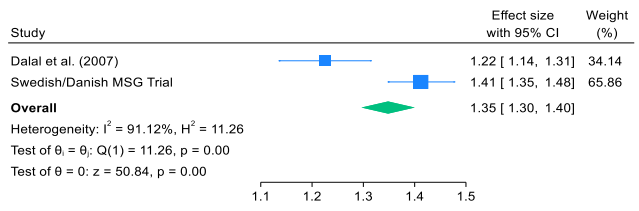


Fixed-effects inverse-variance model

DFS Stage II – 10 years

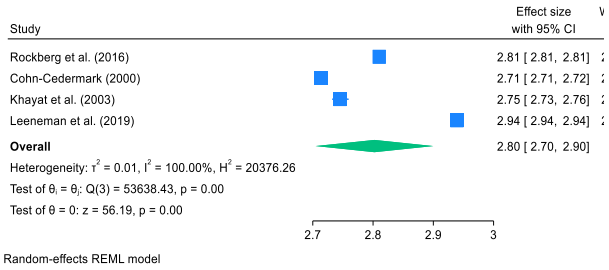


Random-effects REML model

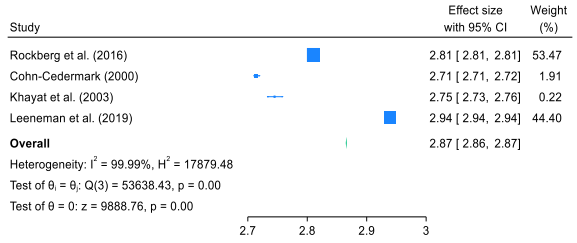


Fixed-effects inverse-variance model

OS Stage I – 2 years

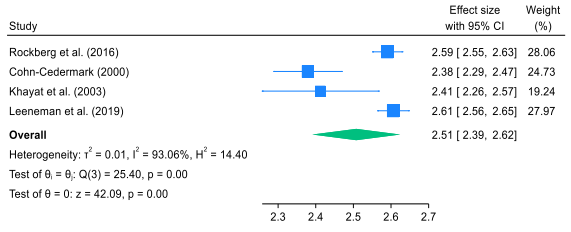


Random-effects REML model

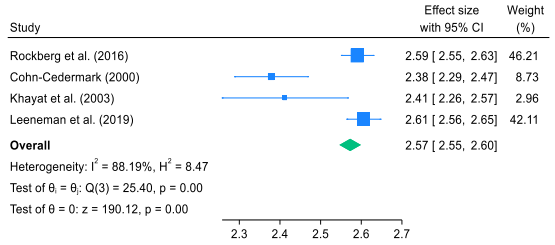


Fixed-effects inverse-variance model

OS Stage I – 5 years

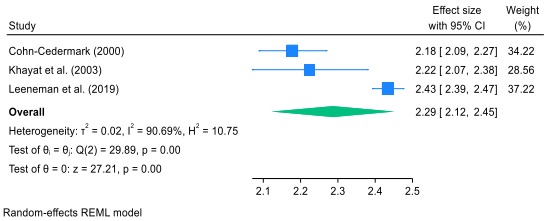


Random-effects REML model

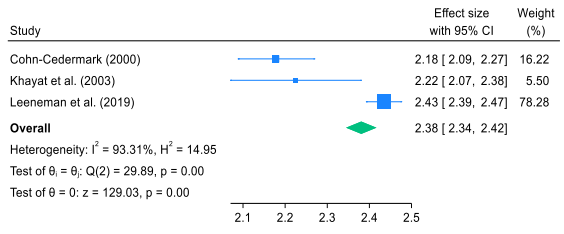


Fixed-effects inverse-variance model

OS Stage 1 – 10 years

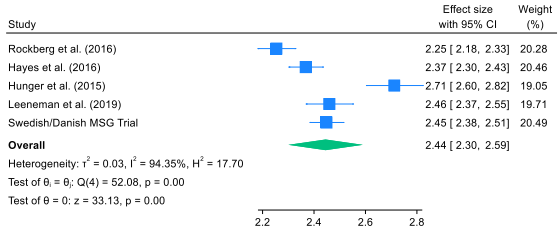


Random-effects REML model

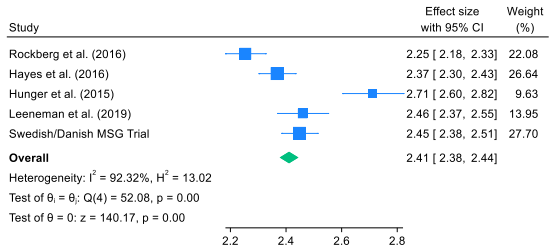


Fixed-effects inverse-variance model

OS Stage II – 2 years

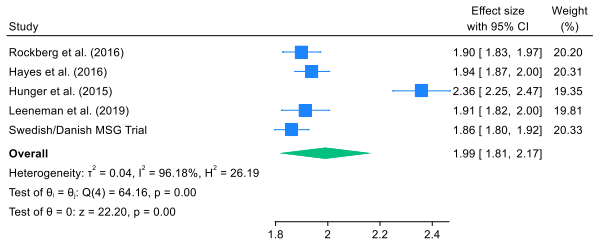


Random-effects REML model

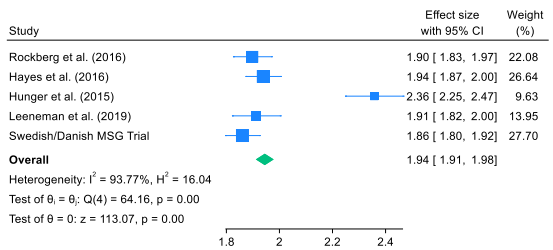


Fixed-effects inverse-variance model

OS Stage II – 5 years

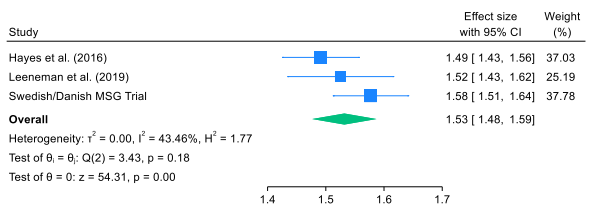


Random-effects REML model

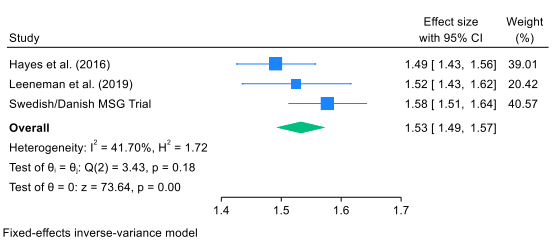


Fixed-effects inverse-variance model

OS Stage II – 10 years



Random-effects REML model

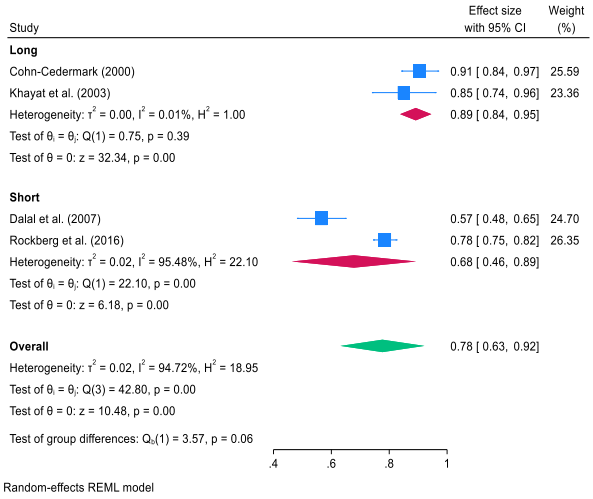


Fixed-effects inverse-variance model

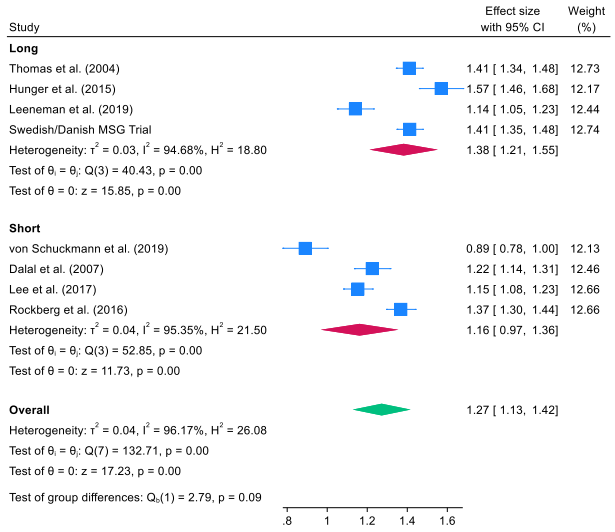
Additional file 4.3: Forest plots from random-effects models: recurrence and follow-up

Median follow-up: (all >5 years were categorized as long follow-up, and all <5 years were categorized as short follow-up)

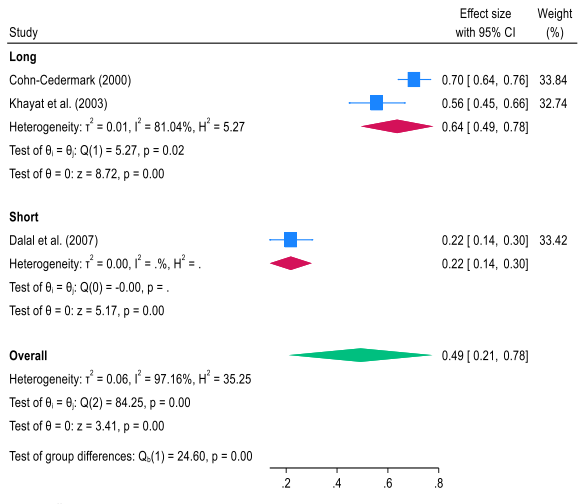
Stage I – Total any recurrence
Long follow-up:
Pooled mean (95% CI): 15.5 (16.6-20.9)
Short follow-up:
Pooled mean (95% CI): 11.1 (5.2-18.5)
Group diff. p = 0.06



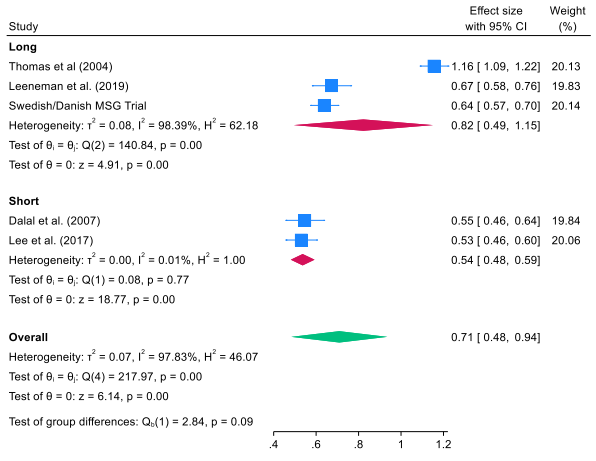
Stage II – Total any recurrence
Long follow-up:
Pooled mean (95% CI): 40.5 (32.4-49)
Short follow-up:
Pooled mean (95% CI): 30 (21.7-39.5)
Group diff. p = 0.09



Stage I – Regional lymph node recurrence
Long follow-up:
Pooled mean (95% CI): 9.9 (5.9-14.5)
Short follow-up:
Pooled mean (95% CI): 1.2 (0.5-2.2)
Group diff. p = 0.00



Stage II – Regional lymph node recurrence
Long follow-up:
Pooled mean (95% CI): 15.9 (5.9-30)
Short follow-up:
Pooled mean (95% CI): 7.1 (5.7-8.5)
Group diff. p = 0.09



Additional file 5.0: Example of spreadsheet for transformations

DFS 2y Stage II

Slår alle studiene sammen til en stor studie:

Utvalgs n	Ikke recurr.	Fått recurr.
310	58,9	251,1
485	119,795	365,205
746	221,562	524,438
900	271,8	628,2
325	54,275	270,725
936	278,928	657,072
3702	**1005,26**	**2696,74**
	P =	**0,7285**
	Var(p) =	5,34328E-05
	SE(p) =	0,007309777
	Nedre CI	Øvre CI
	0,7141	0,7428

Source: Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013;67(11):974-8.*

*Readers who wish to use the equations must correct the error in equation 3, where SE is estimated incorrectly. SE(P) should be $\sqrt{(1/\sum(1/\mathrm{var}(p_i)))}$.

Uten transformasjon

								N-basert vekting		
Studie	p	N	Var (p)	SE(p)	1/ Var(p)	1/ (1/Var(p))	Ivar-basert vek	p / Var (p)	N-baset vekt	Diff vekter	N-vektet skår
von Schuckmann et al. (2019)	0,81	310	0,000496452	0,022281	2 014,3	0,0004965	0,1045	1631,578947	0,08373852	0,0208	0,0678282
Dalal et al. (2007)	0,753	485	0,000383487	0,019583	2 607,7	0,0003835	0,1353	1963,562753	0,13101026	0,0043	0,09865073
Rockberg et al. (2016)	0,703	746	0,000279881	0,01673	3 573,0	0,0002799	0,1854	2511,784512	0,2015127	-0,0161	0,14166343
Thomas et al. (2004)	0,698	900	0,000234218	0,015304	4 269,5	0,0002342	0,2215	2980,13245	0,24311183	-0,0216	0,16969206
Hunger et al. (2015)	0,833	325	0,000428034	0,020689	2 336,3	0,0004280	0,1212	1946,107784	0,08779038	0,0334	0,07312939
Swedish/Danish MSG Trial	0,702	936	0,0002235	0,01495	4 474,3	0,0002235	0,2321	3140,939597	0,2528363	-0,0207	0,17749109
	0,7498333	3702	0,002045571		19 275,0	0,0020456	1,0000	14174,10604			0,728454889
				Var (P) =	0,0000519						
				SE(P) =	0,00720283						

Inverse variance method, P =	**0,7354**	Nedre CI	Øvre CI
SE(P) =	0,00720283	0,7212	0,7495
	Endring CI i %	0,019574	0,0192

Uvektet mean	**0,7498**	Nedre CI	Øvre CI
N-vektet mean	**0,7285**	0,7141	0,7428
	Endring CI i %	0,02006	0,01911

Logit-transformasjon

								N-basert vekting		
Studie	l	N	Var (p)	SE(p)	1/ Var(p)	1/ (1/Var(p))	Ivar-basert vek	p / Var (p)	N-baset vekt	Diff vekter	N-vektet skår
von Schuckmann et al. (2019)	1,4500102	310	0,020960406	0,144777	47,7	0,0209604	0,0659	69,17853546	0,08373852	-0,0179	0,12142171
Dalal et al. (2007)	1,1146769	485	0,011085782	0,105289	90,2	0,0110858	0,1245	100,5501368	0,13101026	-0,0065	0,14603411
Rockberg et al. (2016)	0,8616248	746	0,006420212	0,080126	155,8	0,0064202	0,2150	134,2050224	0,2015127	0,0135	0,17362833
Thomas et al. (2004)	0,8377921	900	0,005271026	0,072602	189,7	0,0052710	0,2619	158,9428984	0,24311183	0,0188	0,20367717
Hunger et al. (2015)	1,6070398	325	0,022118474	0,148723	45,2	0,0221185	0,0624	72,65599827	0,08779038	-0,0254	0,14108264
Swedish/Danish MSG Trial	0,8568399	936	0,005107058	0,071464	195,8	0,0051071	0,2703	167,7756444	0,2528363	0,0175	0,21664024
	1,1213306	3702	0,070962958		724,4	0,0709630	1,0000	703,3082357			1,002484197
			Var (P) =	0,0013804							

l =	**0,971**	Nedre CI	Øvre CI
SE(P) =	0,037154249	0,8981	1,0437
Tilbake transformert til P =	**0,7253**	**0,7105**	**0,7396**
Uvektet mean			
N-vektet mean			

Double arcsine transformasjon DFS Stage II

									N-basert vekting		
Studie	t	N	n (antall recurr)	Var (p)	SE(p)	1/ Var(p)	1/ (1/Var(p))	1/var-basert vekt	p / Var (p)	N-baset vekt	Diff vekter	N-vektet skår
von Schuckmann et al. (2019)	2,2370073	310	251,10	0,003221	0,056750435	310,5	0,0032206	0,0161	694,590761	0,08373852	-0,0676	0,187324
Dalal et al. (2007)	2,1001323	485	365,21	0,00206	0,045384273	485,5	0,0020597	0,0252	1019,61422	0,13101026	-0,1058	0,275139
Rockberg et al. (2016)	1,988275	746	524,44	0,00134	0,036600338	746,5	0,0013396	0,0387	1484,24726	0,2015127	-0,1628	0,400663
Thomas et al. (2004)	1,9774747	900	628,20	0,00111	0,033324078	900,5	0,0011105	0,0467	1780,71594	0,24311183	-0,1964	0,480747
Hunger et al. (2015)	2,296902	325	270,73	0,003072	0,0554274	325,5	0,0030722	0,0169	747,641605	0,08779038	-0,0709	0,201646
Swedish/Danish MSG Trial	1,9862107	936	657,07	0,001068	0,032677296	936,5	0,0010678	0,0486	1860,08634	0,2528363	-0,2042	0,502186
	2,097667	3392		0,01187		3 705,0	0,0118704	0,1922	7586,836124			2,04770479
					Var (P) =	0,0002699						
					SE(P) =	0,016428802						

Fix-effect model

t =	**2,0477**	Nedre CI	Øvre CI
SE(P) =	0,016428802	2,0155	2,0799
t tilbake-transponert til P =	**0,7295354**	**0,7151**	**0,7437**
	Endring CI i %	0,02016	0,01944

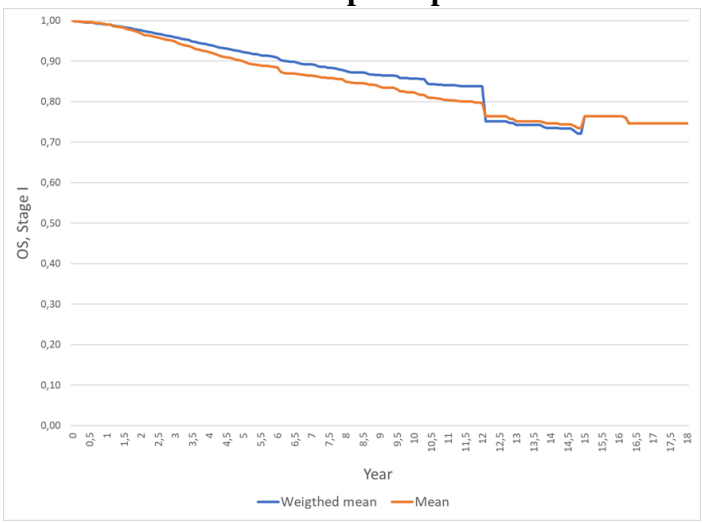
Uvektet mean	**0,7498**	Nedre CI	Øvre CI
N-vektet mean	**0,7285**	0,7141	0,7428
	Endring CI i %	0,02006	0,01911

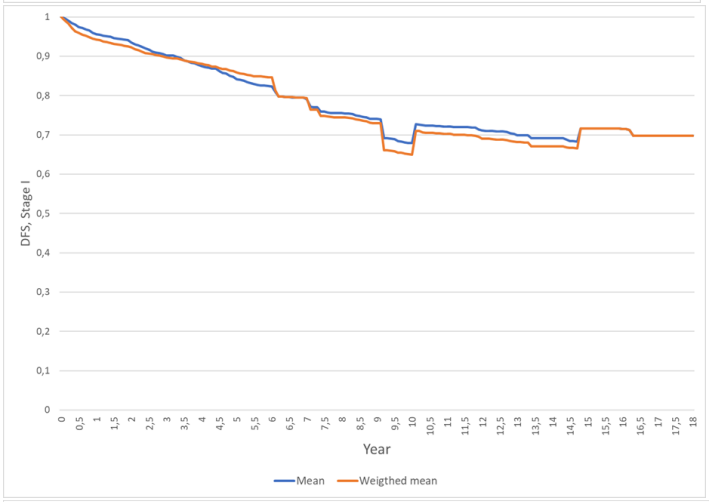
Random-effect REML model. Inndata fra Stata-beregninger

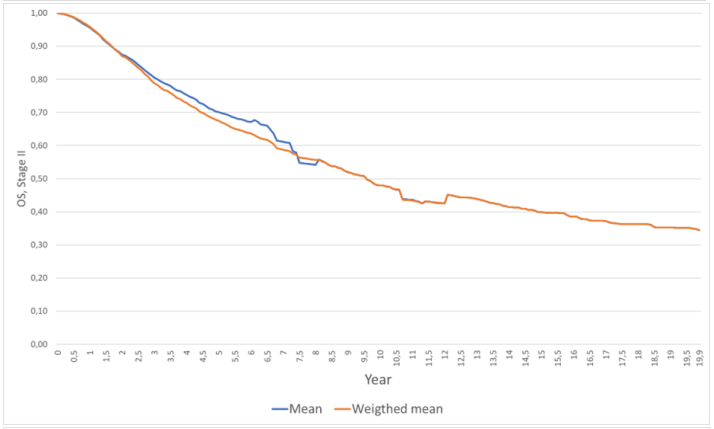
t =	**2,0900**	Nedre CI	Øvre CI
SE(P) =	0	1,9800	2,2000
t tilbake-transponert til P =	**0,74809446**	**0,6989**	**0,7943**

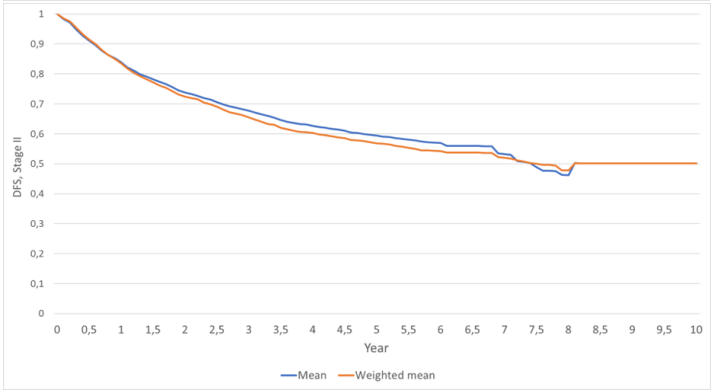
Dette er resultatet for dobbel-sin transfomasjon benyttet i Random-effect modell.

Additional file 6.0: Example of pooled curves unsuitable as OS or DFS survival curves









Additional file 7.0: Excluded studies after quality assessments

Blakely et al. (54) investigated the prognosis and management of thick melanomas (>4.0mm), representing only the extreme end of stage II. This study would have introduced biases upon comparing results to studies encompassing stage II in a more comprehensive manner. McKinnon et al. (60) utilized excision margins as narrow as 1 mm and had an indistinct demarcation between stage I and II, hindering comparability with other studies. Maurichi et al. (59) focused exclusively on T1a+T1b melanomas, omitting T2a (1.01-2.00mm), the extreme end of stage I, potentially leading to biases when comparing with other stage I studies. Akhtar et al. (53) and Kunishige et al. (56) examined safe excision margins solely for melanoma in situ (stage 0 is not included in this systematic review), while Salema et al. (61) adopted a broader approach by considering stage 1 and 2 as a single group, resulting in a somewhat imprecise outcome, thereby complicating its transferability and utility. Hudson et al. (30) was excluded due to its low quality assessment (CASP score: 3/7).

Additional file 8.0: Comparison of different pooling methods for DFS and OS