An updated review of mucosal melanoma: Survival meta-analysis

HYUNG MIN HAHN[1], KYOUNG GEUN LEE[2], WON CHOI[2], SEUNG HYUN CHEONG[2], KI BUM MYUNG[2] and HYUNG JIN HAHN[2,3]

[1]Department of Plastic and Reconstructive Surgery, Ajou University School of Medicine, Suwon, Gyeonggi 16499; [2]Department of Dermatology, College of Medicine; [3]Myunggok Medical Research Institute, College of Medicine, Konyang University, Daejeon, Chungcheongnam 35365, Republic of Korea

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Abstract. Mucosal melanoma (MM) is a highly lethal variant of melanoma that carries a poor prognosis. Extremely low incidence and survival rates have led to few clinical trials, and a lack of protocols and guidelines. The present study performed a survival meta-analysis for the quantitative synthesis of available evidence to search for key patterns that would help clinicians tailor optimal therapeutic strategies in MM. PubMed, EMBASE, Cochrane, MEDLINE, Google Scholar and other databases were searched. Hazard ratios, in disease-specific and overall survival, were calculated for each of the survival-determining variables. MM was 2.25 times more lethal than cutaneous melanoma (CM). The most significant threats to survival were advanced Tumor-Node-Metastasis stage, sino-nasal location, and old age. Chemotherapy was the most effective form of adjuvant therapy. Disease-specific survival, the primary measure of the effect sizes, can fluctuate depending on the accuracy of the reported cause of mortality. In conclusion, MM is a peculiar type of melanoma, with clinical and molecular profile vastly different from the much-familiar CM. In the wake of the era of precision oncology, further studies on driver mutations and oncogenic pathways would likely lead to improved patient survival.

Correspondence to: Professor Hyung Jin Hahn, Department of Dermatology, College of Medicine, Konyang University, 158 Gwanjeodong-ro, Seo-gu, Daejeon, Chungcheongnam 35365, Republic of Korea
E-mail: clemens272@gmail.com

Abbreviations: AJCC, American Joint Committee on Cancer; ALM, acral lentiginous melanoma; CI, confidence interval; CM, cutaneous melanoma; DSS, disease-specific survival; ES, effect sizes; H&N, head and neck; HR, hazard ratio; I2, degree of inconsistency; LDH, lactate dehydrogenase; LVI, lympho-vascular invasion; LRC, loco-regional control; MM, mucosal melanoma; MMHN, mucosal melanoma of head and neck; MSS, melanoma-specific survival; NR, not reported; OC, oral cavity; OS, overall survival; PNI, perineural invasion; PNS, paranasal sinuses; PS, performance score; RCT, randomised controlled trials; RT, radiotherapy; RTK, receptor tyrosine kinase; SN, sino-nasal; UV, ultraviolet

Key words: survival meta-analysis, HR, MM, disease-specific survival, OS

Introduction

Mucosal melanoma (MM) represents a highly aggressive variant of malignant melanoma that arises within the resident melanocytes of mucous linings. Comprising barely one-hundredth fraction of all melanomas, it is an entity that is notorious for the infinitesimal 5-year survival rate (<25%) (1). Although MM is often understood as a blanket term for any extracutaneous melanoma, it nevertheless comes with somewhat hazy disease definition; some authors regard uveal or conjunctival melanomas as bona fide MM, while others are less inclined to label the ocular tumours as such. The head and neck (H&N) is cited as the region most heavily represented (~50%), followed by the ano-rectum, and the female genital tract (FGT) (2). The insidious nature of the disease compounds accurate diagnosis, depriving the affected of any remaining chance for an early detection. Failure to intervene early often boomerangs with the amplified lethality, which is the hallmark of the mucosal disease.

Given the miniscule incidence and patient survival rate, randomised clinical trials (RCT) have been understandably difficult to come by. The resulting paucity of evidence have long clouded our understanding of tumour behaviour. Field clinicians facing therapeutic decisions inevitably suffer from general lack of consensus over virtually all aspects of the disease, from staging to management. While it is tempting to extrapolate from CM-derived data, the notion, that MM is fundamentally a distinctive entity, is now considered canonical (3). Such discrepancies include female preponderance, limited role of UV (ultraviolet) light, and mutation status (4). The different makeup of mutation landscape is thought to be the impetus that drives the divergence between the two (5-7).

In the present meta-analysis and systematic review, the authors present a comprehensive assessment of available evidence to elaborate crucial factors that determine clinical outcome in MM.

Materials and methods

Data collection and inclusion criteria. Literature search was conducted using multiple engines, most notably but not

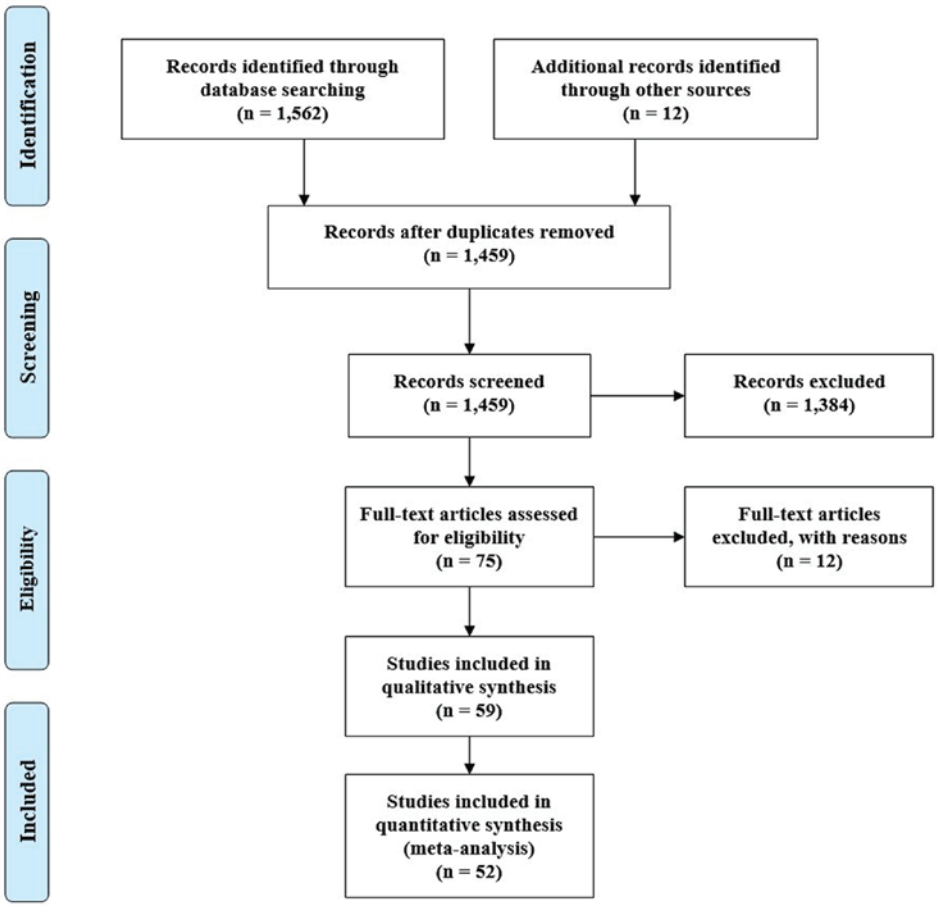


Figure 1. Flowchart of search strategy, adopted from the PRISMA Group, 2009 (10).

limited to, PubMed, EMBASE, Cochrane, MEDLINE, and Google Scholar, up to March of 2018. The query employed various keywords, such as 'mucosal malignant melanom', 'anorectal melanoma', 'sino-nasal melanoma' and 'survival'; the search was intended to include any abstract proceedings or graduate theses [www.thesis.de], so as not to discount 'grey' literature from the study. No restriction was applied in terms of the language of publication. The following criteria were considered for selection: i) primary mucosal melanomas, ii) reporting of Kaplan-Meier survival analysis results, or iii) Cox regression analysis with time-to-event information. Where HR were not explicitly given, they were imputed using the method described by Tierney *et al* (8). Excluded were studies i) on leptomeningeal melanomatosis, ii) based on cell lines iii) performed on canine, murine or other non-human subjects. The present study was conducted in accordance to the Meta-analysis of Observational Studies in Epidemiology guidelines for the reporting of meta-analyses of observational studies (MOOSE) (9).

Statistical analysis. The principal parameter of effect size (ES) reporting used in the study was hazard ratio (HR), in terms of melanoma-specific survival (=disease-specific survival, DSS) and overall survival (=all-cause survival, OS). The main surrogate for detecting between-study heterogeneity was the I^2 statistic. The assumption of homogeneity was considered valid if I^2 was <50%, in which cases the fixed effect model was used; for all other cases, the random effect model was used. Before incorporating a study into analysis, sensitivity testing was performed to decide if there was a pulling effect by single studies with substantial weight. Publication bias was assessed with funnel plots and Egger test. Statistical analyses were carried out with Comprehensive Meta-Analysis Software (v3.0; Biostat, Englewood, NJ, USA). $P<0.05$ were considered to indicate a statistically significant difference.

Results

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (10) flow diagram of the search strategy, and characteristics of the included studies are given in Fig. 1 and Table I, respectively. Search query using the aforementioned keywords initially returned 1,459 articles from 8 different databases, of which 52 were deemed to suit our agenda. All the studies originated from three continent regions: North/Central America (18, 34.6%), Asia/Indian subcontinent/Oceania (21, 40.4%), and the European Union (13, 25.0%). Topographically, 27 studies (51.9%) were on head and neck region (MMHN), 4 (7.7%) on gastrointestinal tract, 3 (5.8%) on urinary/female genital tract, and 18 (34.6%) on all mucosal sites. Potential survival variables were arbitrarily categorised into three groups: i) host factors, which is demographic characteristics of the affected individual, ii) tumour factors, relating to various aspects of tumour histology, behaviour, and staging, and iii) treatment factors, which are parameters that assess the impact of differing treatment modalities on survival.

Table I. Characteristics of included studies.

Author, year	Country[b]	Location	No. of patients	Follow-up	Ref.
Abugideiri *et al*, 2016	USA	H&N	39 (SRT=27; S=12)	Median 8.1 years	17
Ahn *et al*, 2010	Korea	H&N	32 (SRT=16; S=16)	Median 25.3 months	18
Aiempanakit *et al*, 2018	Thailand	All mucosal	17 (S=14, UN=3)	Median 18.2 months	19
Ajmani *et al*, 2017	USA	SN	704 (SRT=399; S=305)	NR	20
Amit *et al*, 2018	USA	SN	198 (SRT=81; S=79; SCRT=24; C or CRT=14)	Median 26 months	21
D'Angelo *et al*, 2016	USA	All mucosal	889 (ipilimumab and nivolumab)	6.2 months	22
Benlyazid *et al*, 2010	France	H&N	160 (SRT=78; S=82)	Median 65.2 months	23
Bishop and Olszewski 2014	USA	All, including CM[a]	229,976 (NR)	NR	24
Chiu and Weinstock, 1996	USA	OC	40,320 (NR)	NR	25
Ciarrocchi *et al*, 2017	Italy	Anorectum	208 (SRT=32; S=167)	Median 14 months	26
Ercelep *et al*, 2016	Turkey	All mucosal	229,976 (NR)	Median 27 months	27
Harada *et al*, 2016	Japan	Oesophagus	10 (S=10)	NR	28
Hasebe *et al*, 2017	Japan	H&N	85 (RT=85)	Median 42.5 months	29
Heinzelmann-Schwarz *et al*, 2014	Australia	Vulva	33 (NR)	NR	30
Heppt *et al*, 2017	Germany	All mucosal	444 (NR)	NR	31
Hughes *et al*, 2013	Australia	All, including CM[a]	485 (Lymphadenectomy)	Median 17.4 months	32
Jang *et al*, 2014	Korea	All, including CM[a]	206 (S=197; C=46; RT=31)	NR	33
Kang *et al*, 2018	China	All mucosal	60 (NR)	Median 36 months	34
Khan *et al*, 2014	USA	SN	567 (NR)	NR	35
Kirchoff *et al*, 2016	USA	All mucosal	227 (S=53; S + other=174)	NR	36
Kirschner *et al*, 2013	USA	Vagina	201 (SRT=53; S=87; RT=30)	Median 14 months	37
Kong *et al*, 2016	China	All, including CM[a]	412 (NR)	Median 31 months	38
Konuthula *et al*, 2017	USA	SN	695 (SRT=271; S=206; SC=29; SCRT=49; C=21; RT=42)	NR	39
Koto *et al*, 2017	Japan	H&N	260 (RT=105; CRT=155)	Median 22 months	40
Kuk *et al*, 2016	Korea	OC	39 (S=22; S + C or RT=17)	NR	41
Lansu *et al*, 2018	Netherlands	SN	63 (SRT=63)	Median 23 months	42
Lawaetz *et al*, 2016	Denmark	H&N	98 (SRT=26; S=49; SC=2; SCRT=2; RT=8; None=8)	Median 24.5 months	43
Lee *et al*, 2017	Korea	H&N	31 (SRT=13; S=9; SC=7; SCRT=2)	Mean 9 months	44
Lee *et al*, 2017	USA	OC	232 (NR)	NR	45
Lombardi *et al*, 2016	Italy	SN	58 (SRT=13; S=42; SCRT=3)	Median 30 months	46
Mücke *et al*, 2009	Germany	OC	10 (NR)	NR	47
Nakamura *et al*, 2018	Japan	All mucosal	45 (checkpoint inhibitors)	NR	48
Oba *et al*, 2011	Japan	All, including CM[a]	78 (NR)	Median 40 months	49
Pandey *et al*, 2002	India	H&N	60 (SRT=6; S=17; SC=3; SCRT=1; C=8; RT=7)	NR	50
Pfeil *et al*, 2011	Germany	All mucosal	172 (NR)	Median 24 months	51
Plavc *et al*, 2016	Slovenia	H&N	61 (SRT=14; S=17; C=1; RT=15)	Median 16.5 months	52
Roh *et al*, 2016	Korea	All mucosal	392 (NR)	Mean 55.4 months	53
Samstein *et al*, 2016	USA	SN	78 (SRT=64; S=14)	Median 21 months	54

Table I. Continued.

Author, year	Country[b]	Location	No. of patients	Follow-up	Ref.
Sanchez *et al*, 2016	USA	Genitourinary tract	1,586 (NR)	NR	55
Schaefer *et al*, 2017	Germany	All mucosal	75 (checkpoint inhibitors)	NR	56
Schmidt *et al*, 2017	USA	H&N	1,368 (SRT=704; S=566; RT=98)	Median 55.2 months	57
Shoushtari *et al*, 2017	USA	All mucosal	81 (NR)	NR	58
Shuman *et al*, 2011	USA	H&N	52 (SRT=15; S=13; SC=18; NR=6)	Median 97 months	59
Song *et al*, 2016	China	OC	62 (NR)	Median 32.5 months	60
Sun *et al*, 2014	China	SN	65 (SRT=13; S=18; SC=9; C=6; RT=4; CRT= 2)	NR	61
Tchelebi *et al*, 2016	USA	Rectum	63 (SRT=18; S=45)	Median 17 months	62
Thariat *et al*, 2011	France	SN	155 (NR)	Median 37 months	63
Wang *et al*, 2013	China	OC	81 (NR)	NR	64
Wen *et al*, 2017	China	All mucosal	52 (checkpoint and PD-1 inhibitors)	NR	65
Won *et al*, 2015	Korea	SN	155 (NR)	NR	66
Yeh *et al*, 2006	USA	Anorectum	46 (S=23; C=23)	Median 29 months	67
Yi *et al*, 2011	Korea	All, including CM[a]	95 (NR)	Median 41 months	68

[a]Included for purpose of comparison with mucosal melanoma; [b]For multi-national groups, only the nationality of 1st author was listed. H&N, head and neck; SN, sino-nasal; CM, cutaneous melanoma; OC, oral cavity; S, surgery only; C, chemotherapy only; RT, radiotherapy only; SRT, surgery plus radiotherapy; SC, surgery plus chemotherapy; CRT, chemotherapy plus radiotherapy; SCRT, surgery plus chemotherapy plus radiotherapy; NR, not reported.

Host factors

Age. With respect to younger individuals (<50 years), the HR for those in the seventh decade of life was 1.3 (HR=1.31; 95% CI, 1.19-1.45; P=0.00). The disease-specific hazards for patients in their 70's were 1.7 (HR=1.69; 95% CI, 1.62-1.77; P=0.00). A similar pattern was seen with overall survival. There was no evidence of heterogeneity in any of the subgroups (Fig. 2).

Sex. The HR for males was calculated to be 1.1 (HR=1.11; 95% CI, 0.93-1.31; P=0.26). The value was similar for OS (HR=1.12; 95% CI, 1.03-1.23; P=0.01). No statistical heterogeneity was found (I^2=32.14).

Ethnicity. Pooled HR, with non-Hispanic white Caucasians as reference, was computed for patients with African, Asian/Pacific Island, and other (including white Hispanic, Native American and Mestizos) ancestries. Compared to Caucasian individuals, the hazard to overall survival for non-Caucasians as a whole was ~1.4 (HR=1.39, 95% CI, 1.06-1.82; P=0.02). Apart from the overall death risk, ethnicity of the affected per se did not have seem to be a major influence on survival (Table II).

Comorbidities and 'High-risk' lifestyle. Having one or more major comorbidities showed a weak correlation to increased risk in all-cause mortality (HR=1.43, 95% CI, 1.01-2.04; P=0.04). On the other hand, the mode of life traditionally considered 'high-risk'-e.g., sedentariness, obesity, smoking-was found to be a significant threat to neither disease-specific (HR=1.41, 95% CI, 0.98-2.03; P=0.07) nor overall (HR=1.24, 95% CI, 0.98-1.56; P=0.14) survival.

Tumour factors

Cutaneous melanoma. The relative lethality of MM vs. CM was 2.25 (HR=2.27, 95% CI, 1.96-2.62; P=0.00). No significant heterogeneity was detected across the studies (I^2=26.41; Fig. 3).

Location. A primary lesion originating within the sino-nasal (SN) cavity was found to be 1.4 times more deadly compared to other locations (HR=1.44; 95% CI, 1.28-1.63; P=0.00). The HR for OS was nearly 2.0 (HR=1.93; 95% CI, 1.59-2.33; P=0.00). Head and neck lesions (MMHN) as a whole showed an HR of 1.4 (HR=1.35; 95% CI, 1.02-1.79; P=0.00) for overall survival.

Multifocal disease. MM is a devastating cancer partly because of its tendency to arise from multiple foci. The associated disease-specific death risk was nearly 3.0 (HR=2.95; 95% CI, 2.72-3.19; P=0.00).

Clinical staging (MMHN). The TNM staging system, developed by the American Joint Committee on Cancer (AJCC), is one of the most widely accepted standards for MMHN staging and conventionally the most accurate predictor of survival. T4 disease (T4a and T4b) was 2.4 times more fatal than T3 tumours (95% CI, 1.75-2.98; P=0.00). Meanwhile, N1 disease had an HR of 2.0 compared to N0 (HR=1.90; 95% CI, 1.62-2.23; P=0.00). For metastatic diseases (M1), the HR was 3.2 (HR=3.17; 95% CI, 2.72-3.70; P=0.00; Fig. 4).

Clinical features/Macro-morphology. Elevated lactate dehydrogenase (LDH) level was associated with the greatest HR for disease-specific survival (HR=2.06; 95% CI, 1.56-2.72; P=0.00). Higher performance score (PS) was correlated with increased risk for OS (HR=1.71; 95% CI, 1.32-2.21; P=0.00).

Table II. Hazard ratios for non-Caucasian ethnicities.

Ethnicity comparison	Survival	No. of studies	Pooled HR	95% CI	Z-value	P-value	I^2
Non-Caucasian vs. Caucasian	DSS	5	1.12	1.05-1.20	3.354	0.001	0.0001
Non-Caucasian vs. Caucasian	OS	3	1.39	1.06-1.82	2.358	0.018	0.0001
Afro-American vs. Caucasian	DSS	6	1.13	0.95-1.34	1.421	0.155	4.451
API vs. Caucasian	DSS	2	1.09	0.80-1.49	0.563	0.574	91.47

HR, hazard ratio; CI, confidence interval; DSS, disease-specific survival; OS, overall survival; API, Asian and Pacific Islander.

Table III. Hazard ratios for clinical/macro-morphological features.

Feature comparison	Survival	No. of studies	Pooled HR	95% CI	Z-value	P-value	I^2
Elevated LDH vs. WNL	DSS	4	2.06	1.56-2.72	5.104	0.001	0.001
PS>1 vs. PS<0	OS	4	1.71	1.32-2.21	4.112	0.001	0.001
Ulceration vs. no ulceration	DSS	3	1.32	0.91-1.90	1.465	0.143	6.401
Ulceration vs. no ulceration	OS	4	1.44	1.04-2.01	2.191	0.215	32.95
Pigmentation vs. no pigmentation	OS	3	0.93	0.70-1.25	0.464	0.642	0.001
Necrosis vs. no necrosis	DSS	2	1.29	0.96-1.73	1.708	0.088	0.001
Necrosis vs. no necrosis	OS	2	0.96	0.55-1.68	0.013	0.989	72.12

LDH, lactate dehydrogenase; PS, performance score HR, hazard ratio; CI, confidence interval; DSS, disease-specific survival; OS, overall survival.

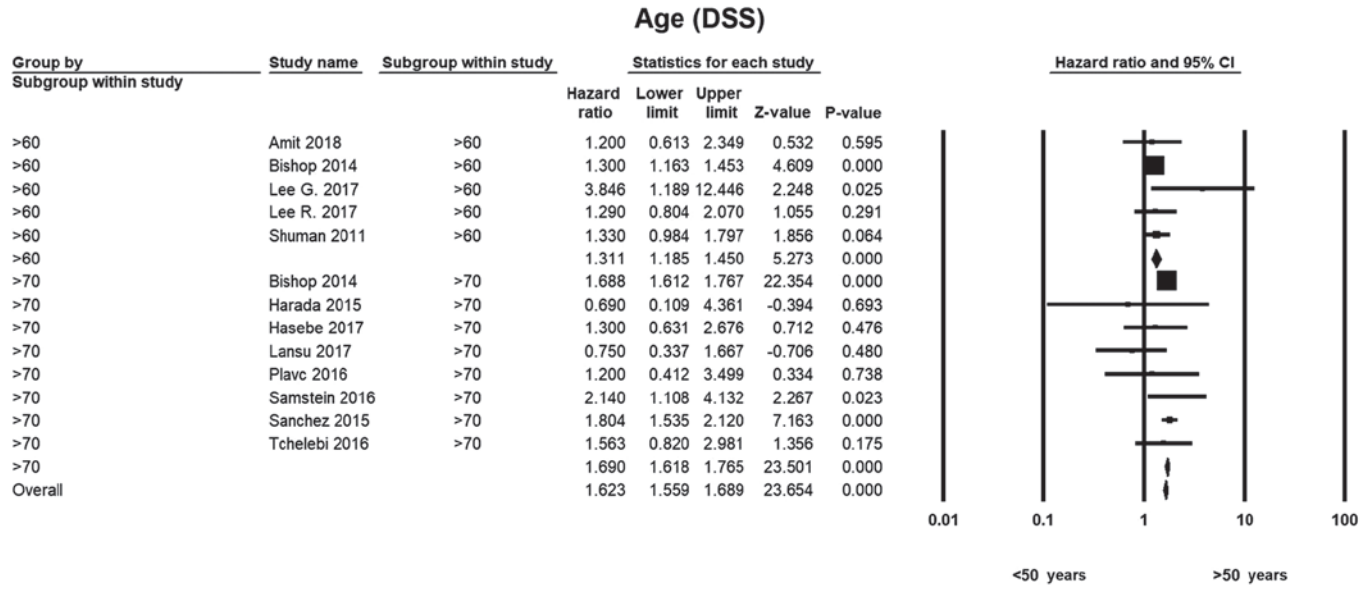


Figure 2. Forest plots for advanced age. DSS, disease-specific survival; CI, confidence interval.

Ulceration of primary lesions was also linked to unfavourable OS. The verdict on pigmentation (HR=0.87; 95% CI, 0.66-1.15; P=0.34), necrosis, and nodularity of primary tumours was inconclusive (Table III).

Microscopic features. Margin status was the most important micro-morphological determinant of survival. The HR attributed to margin positivity was nearly 2.0 (HR=1.85; 95% CI, 1.34-2.54; P=0.00). The effect of perineural invasion (PNI) and lympho-vascular invasion (LVI) was not statistically significant. Meanwhile, Breslow thickness, depth of invasion, and mitotic count did not seem to play a significant role in either terms of survival (Table IV).

Treatment factors

Extent of treatment. Radical operation was found to amplify overall death risk by 2.5 (HR=2.61; 95% CI, 2.04-3.34;

Table IV. Hazard ratios for microscopic features.

Feature comparison	Survival	No. of studies	Pooled HR	95% CI	Z-value	P-value	I^2
(+) Margin vs. (-) margin	DSS	10	1.85	1.34-2.54	3.759	0.001	23.84
(+) Margin vs. (-) margin	OS	10	1.59	1.21-2.08	3.365	0.001	44.22
Breslow >1 mm vs. Breslow <1 mm	DSS	6	1.07	0.99-1.19	1.755	0.079	29.63
Breslow >1 mm vs. Breslow <1 mm	OS	3	1.07	0.99-1.17	1.621	0.105	11.23
Invasion >2 mm vs. invasion <2 mm	DSS	3	2.02	0.68-6.03	1.259	0.208	81.02
Invasion >2 mm vs. invasion <2 mm	OS	4	2.02	1.26-0.23	2.913	0.004	0.001
Mitosis (+) vs. mitosis (-)	DSS	4	1.09	1.03-1.15	2.875	0.004	0.001
Mitosis (+) vs. mitosis (-)	OS	4	1.06	1.01-1.12	2.405	0.016	0.001
PNI vs. PNI (-)	DSS	2	2.08	0.97-4.4	1.884	0.06	42.65
Lymphovascular invasion vs. no invasion	DSS	3	1.24	0.94-1.64	1.537	0.124	0.001
Epithelioid type vs. non-epithelioid	DSS	3	1.29	0.94-1.78	1.561	0.118	0.001

PNI, perineural invasion; HR, hazard ratio; CI, confidence interval; DSS, disease-specific survival; OS, overall survival.

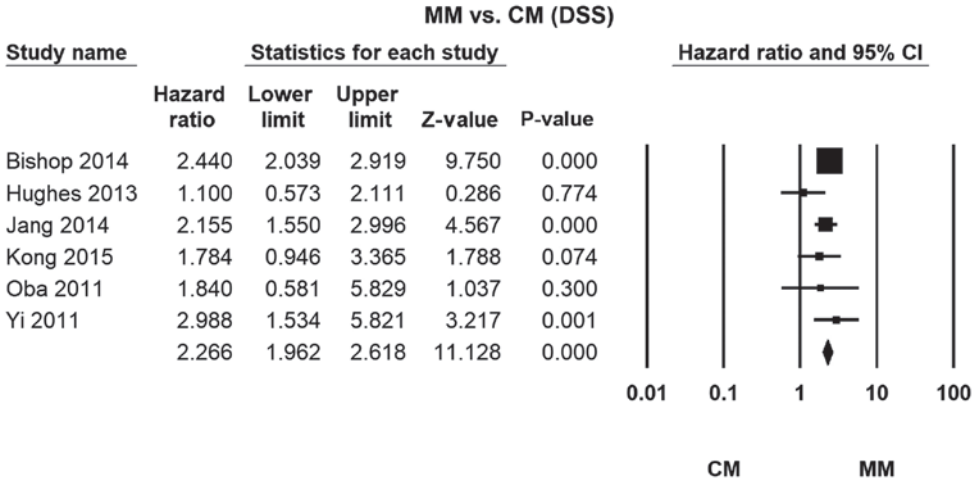


Figure 3. Forest plots for the lethality of mucosal melanoma vs. cutaneous melanoma (DSS). MM, mucosal melanoma; CM, cutaneous melanoma; DSS, disease-specific survival; CI, confidence interval.

P=0.00); When surgery was the sole modality of treatment, it was associated with a significant risk elevation in both terms of survival (HR of 1.72 and 2.21, respectively). Conversely, when any modality but surgery was used, similar increase in mortality was observed. For therapeutic regimen consisted entirely of chemotherapy, the attributed risk in mortality was around 1.5. Meanwhile, radiotherapy (RT) apparently carried the least detriment to patient survival as monotherapy.

The value of lymphadenectomy for primary tumours in the cephalo-cervical subsite was dubious (HR=0.86; 95% CI, 0.73-1.02; P=0.07). Likewise, endoscopic resection showed neither inferior nor superior results compared to the more traditional approach in terms of survival benefit (P=0.83 and 0.68, respectively; Table V).

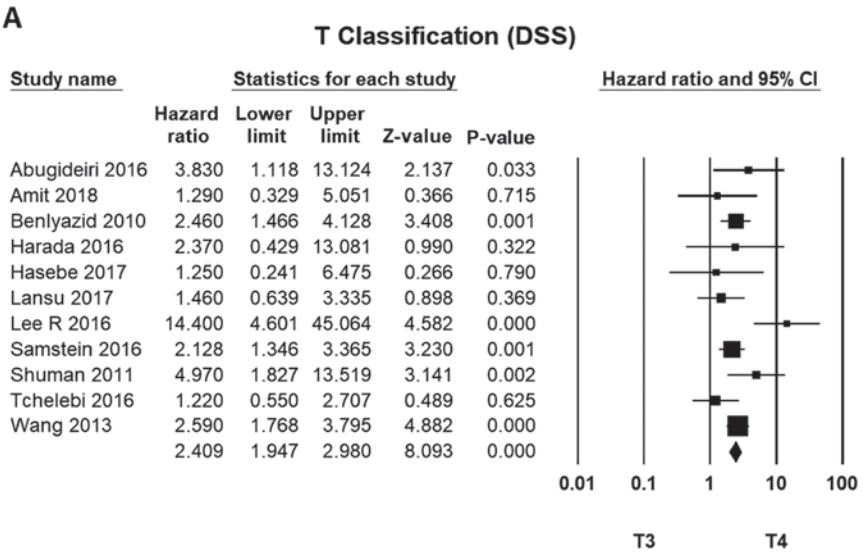
Adjuvant therapy. Adjuvant chemotherapy was found to reduce both disease-specific and overall death by some 30 percent. The therapeutic regimen included cisplatin/tamoxifen, dacarbazine (DTIC), and interferon-γ (INF-γ). RT, while also significantly effective, tended to be somewhat less efficacious (HR=0.84; 95% CI, 0.82-0.86; P=0.01; Fig. 5).

Immunotherapy. Immunotherapy, usually involving PD-1 (programmed death protein-1), immune checkpoint inhibitors (e.g., CTLA-4), or a combination of the two, was shown to more effective for MM than CM. The pooled HR was 0.49 (95% CI, 0.37-0.65; P=0.00; Fig. 6) for overall survival. No inter-study heterogeneity was found across the studies (I^2=0.00).

Discussion

The present meta-analysis had aimed to provide an updated review on various aspects of MM, with data from the most recent studies. The genetic and molecular underpinning behind the distinctive biologic behaviour is believed to stem from amplification of c-*Kit* (11), a receptor tyrosine kinase (RTK). In contrast, b-*Raf* and n-*Ras* mutations are infrequent in MM. This oncogenic mutation profile is reminiscent of the acral lentiginous subtype of CM (ALM). Quite fittingly, ALM shares several characteristics with MM in common, namely i) infrequency (1-2% of all CM), ii) delayed detection and hence worse prognosis, and iii) relative preponderance in non-Caucasian ethnic groups.

A



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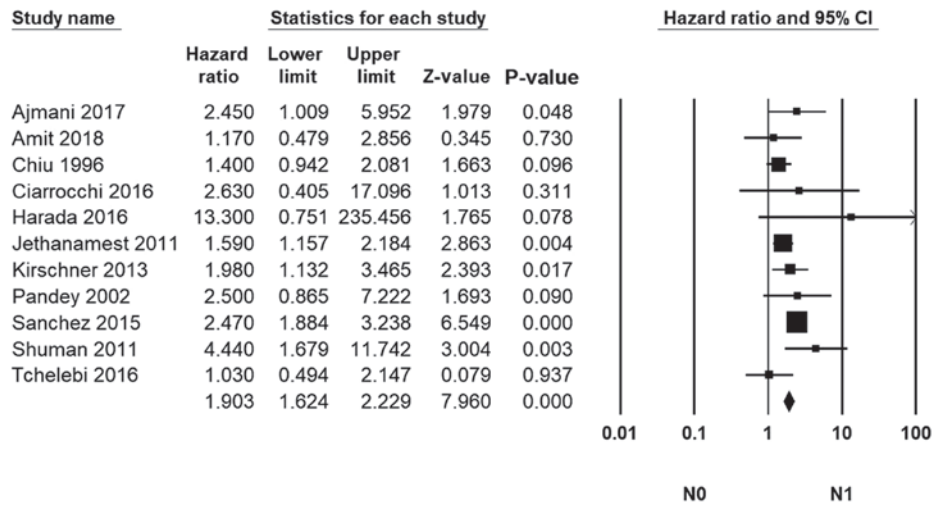

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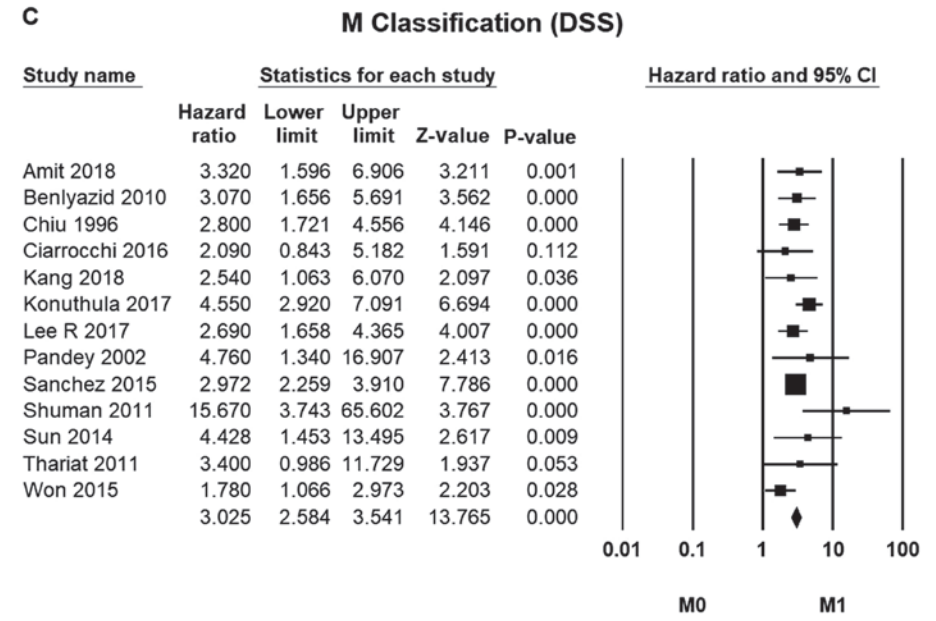

Figure 4. Forest plots for TNM staging (DSS): (A) T4 vs. T3 disease, (B) N1 vs. N0 disease, and (C) M1 vs. M0 disease. DSS, disease specific survival; CI, confidence interval; TNM, tumor-node-metastasis.

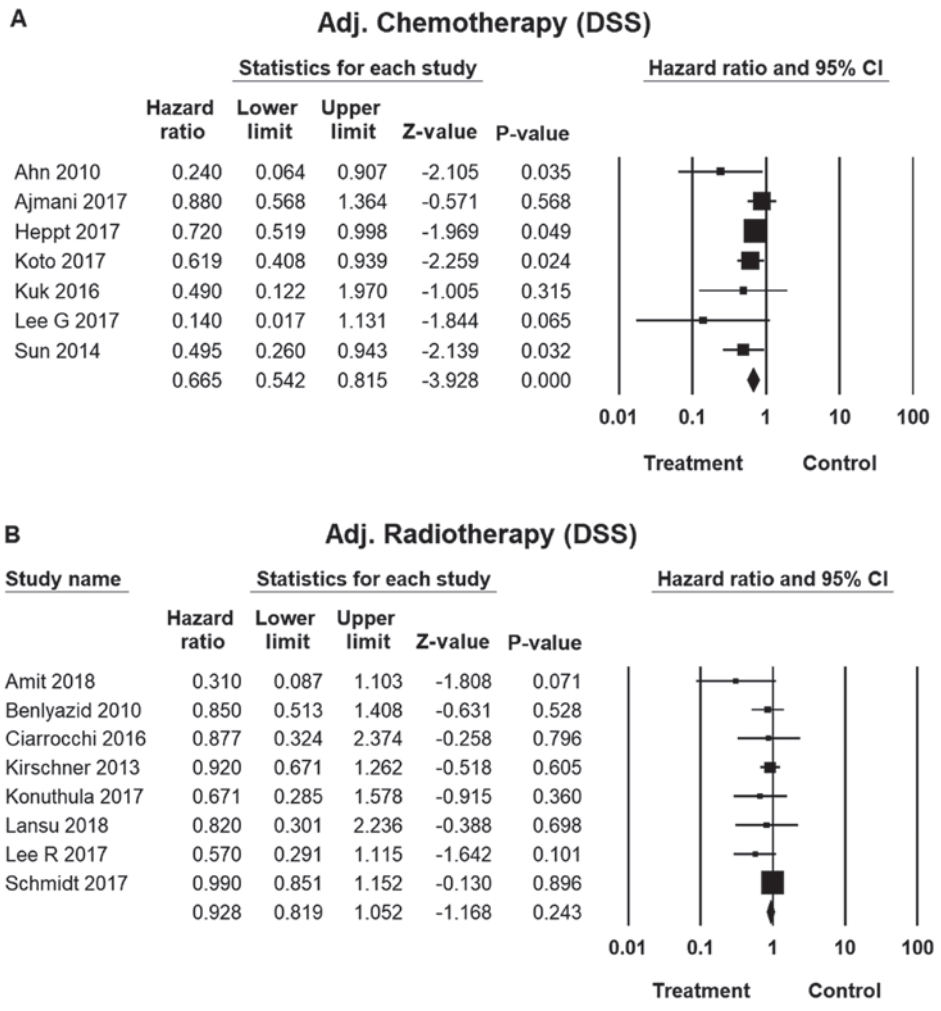

Figure 5. Forest plots for adjuvant therapy (DSS): (A) Chemotherapy and (B) radiation therapy. DSS, disease-specific survival; CI, confidence interval; Adj., adjuvant.

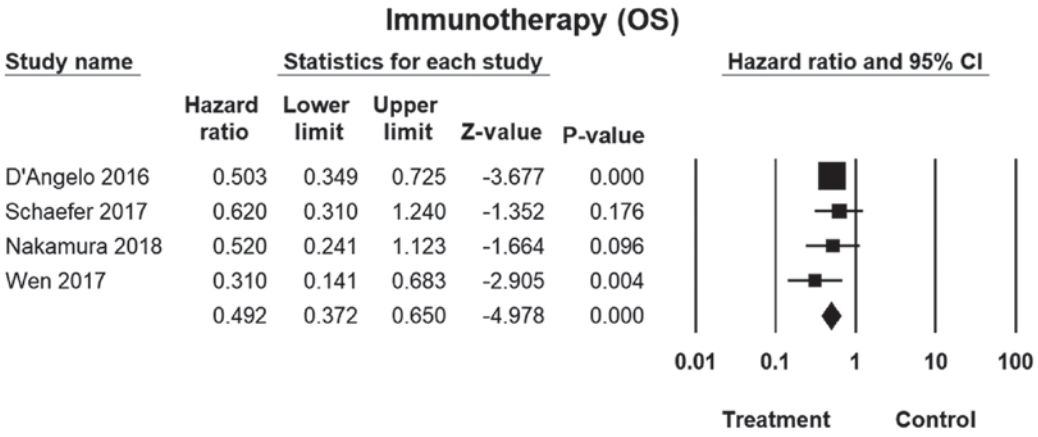

Figure 6. Forest plots for immunotherapy (OS): CI, confidence interval; OS, overall survival.

Although what is known about MM pales in comparison to the cutaneous disease, a few generalities can be drawn from our analysis: in the authors' estimation, MM was two-and-a-quarter times more life-threatening than CM. As a whole, the influence of the 'host factors' was not imposing; one pattern that stood out was advanced age. The median age of onset for MM is higher than CM, at 67 years (vs. 55 years for CM). The death risk in this age group was more than 1.5, compared to the younger cohort (<50 years), which might partially account for the higher mortality. While the incidence tends to be higher and the prognosis grimmer for male melanoma patients in general, MM is an exception; it is reasonably well established that MM shows predilection for females (12). Moreover, there seemed to be no respect of sexes with MM when it comes to mortality, although

Table V. Hazard ratios for different modalities of treatment.

Modality comparison	Survival	No. of studies	Pooled HR	95% CI	Z-value	P-value	I^2
Radical op. vs. Conservative Tx	OS	5	2.61	2.04-3.34	15.079	0.001	55.35
Op. alone vs. SC/SRT	DSS	11	1.78	1.55-2.05	8.192	0.001	30.85
RT alone vs. SRT	DSS	5	1.29	1.08-1.54	2.831	0.005	19.37
RT alone vs. SRT	OS	4	1.52	1.35-1.70	7.087	0.001	26.97

Op., operation; RT, radiotherapy; SC, surgery plus chemotherapy; SRT, surgery plus radiotherapy; HR, hazard ratio; CI, confidence interval; DSS, disease-specific survival; OS, overall survival.

male individuals may be at a slight disadvantage as far as overall survival is concerned. MM is also peculiar from ethnic perspectives because the higher proportion of non-Caucasian patients (especially African and Asian races) (13) is higher. This point is underlined by the fact that 40% of the referenced studies came from regions where the indigenous population is not of white Caucasian ancestry. Nevertheless, racial disparities did not appear to be a major deciding factor in MM-specific mortality. The higher all-cause mortality for non-white cohorts may point to either supposedly superior overall quality of care in Western facilities, or a legitimate, ethno-genetic differences in the ability of the body system to cope with the cancer or mount anti-tumour immune defence against. The fact that undesirable health-related behaviours played negligible role in survival may be one indication that the intrinsic cancer behaviour wields an overriding influence above other variables.

Mucosal melanoma of the head and neck (MMHN), cited as the most common location of MM occurrence overall, also carried the worst prognosis. Tumours in the paranasal sinuses (PNS)-maxillary and ethmoid, etc.-predisposed the individuals to significantly higher disease-specific and overall mortality, with the latter perhaps reflecting the inaccessibility of the subsite, rendering it all the more unfeasible to carry out effective surgical manoeuvres. Tumour thickness would normally be one of objective prognosticators for solid organ cancers. That said, the usefulness of the AJCC clinical stageing system in CM cannot be readily engrafted into mucosal patients, the reason for which is questionable validity of tumour thickness as a prognostic index (14). This notion has been backed by the authors' findings, that neither thickness nor depth of invasion is a significant determinant of survival (Table IV).

Although surgery constitutes the backbone of management strategy in many cases, radical excision seems to be a poor choice of treatment for the considerable morbidity and added mortality associated. Any mono-modality therapy was shown to increase death risk by at least 1.5. For inoperable cases, immunotherapeutic regimen, usually consisting of combination of CTLA-4 and PD-1 inhibitors (e.g., nivolumab and ipilimumab), may be the most rational option. Also, both chemotherapy and radiotherapy were found to be survival-benefitting adjuvant modalities. However, as of now, there is no clearly established formula for specific combination of for chemotherapeutic agents and anti-tumour biologics (‘cocktails’).

The current study was hampered by a few limitations. The validity of disease-specific survival (DSS), the primary measure of effect sizes, is grounded on the premise of the reported cause of death being accurate. This inherent risk can potentially be a limiting factor with cancers such as MM, in which the high lethality can often obscure the true cause of death. In addition, all but two of the included studies came out after the year 2010. This is mainly due to the rarity of the disease, with many studies taking several decades to complete.

In summing up, mucosal melanoma is a highly malignant entity that is difficult to detect, treat, and even study. It is accentuated by an oncogenic profile that is at odds with the more prevalent cutaneous disease. Microscopic frequency, coupled with air of pessimism surrounding the gross ineffectuality of conventional arsenal, may have pushed it into relative obscurity and disinterest. Nonetheless, a body of recent evidence indicates its incidence is on the rise (15,16), and may well be on its way to becoming a force to be reckoned with. Further studies, elaborating on the oncogenic pathways and driver mutations, are needed to improve the overall outlook of this fearsome cancer, especially now that the era of three P's-precision, personalized, and preventive oncology-is looming over the horizon.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HMH and KGL designed and conducted the study. HJH and KGL produced the manuscript. WC, KGL, HJH, HMH, SHC and KBM performed the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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