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# The prognostic value of regression change in melanoma

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**Abstract**

**Background:** Regression in melanoma refers to an immune-mediated partial or whole vanishing of various tumor cells. It is important to note that regression is a common histopathological finding, but its prognostic significance is very controversial. This meta-analysis aims at evaluating the prognostic value of regression in cutaneous melanoma patients.

**Methods:** A literature search will be undertaken across various electronic databases. The databases include PubMed, Embase, Web of Science, and Cochrane Library for studies published up to October 2024. Notably, it will include studies that investigated the existing relationship between histological regression and patient outcomes in melanoma. Studies reporting various hazard ratios (HRs) and sufficient data to calculate risk estimates for survival outcomes will be included. Various random-effects models will be applied in calculating pooled effect estimates.

**Results:** Ten studies involving 3,782 melanoma patients attained the inclusion criteria. The presence of regression was not significantly related to overall survival (OS) (HR is equal to 0.87, 95% CI: 0.69-1.10, p = 0.24). The regression revealed a significant association with improved disease-free survival (DFS) (HR is equal to 0.72, 95% CI: 0.58-0.89, p is equal to 0.003). Subgroup analysis revealed that extensive regression (is more than 50% of tumor area) was related to better prognosis (HR is equal to 0. 65, 95% CI: 0.48 - 0.88, p is equal to 0.006) compared to partial regression. Regression in thin melanomas (is less than or equal to 1 mm) revealed a more substantial protective effect (HR is equal to 0.61, 95% CI: 0.45 - 0.83, p is equal to 0.002) than in thick melanomas.

**Conclusions:** The meta-analysis suggests that regression in melanoma, especially extensive regression in thin melanomas, is related to improved disease-free survival. Therefore, the findings challenge the traditional view that regression represents a negative prognostic factor. It also challenges the suggestion that the extent of regression and tumor thickness are important considerations when evaluating its prognostic impact. Further prospective studies with standardized regression assessment criteria are essential in validating the findings.

**Keywords:** Melanoma, regression, prognosis, survival, meta-analysis

## Introduction

Cutaneous melanom the most violent skin cancer forms. Notably, it has recorded increasing incidence rates worldwide [1]. Melanoma has been attributed to the common skin cancer-related demises despite various advances in detection and treatment. Notably, it has recorded a 5-year existence rate dropping significantly once metastasis occurs, as stated by [2]. Therefore, accurate determination of prognosis is crucial as it will help ensure appropriate patient management, treatment planning, and clinical trial design.

Histological regression in melanoma refers to the partial and complete disappearance of tumor cells. It is accompanied by inflammatory infiltrate, melanophages, fibrosis, vascular proliferation, and epidermal attenuation, as stated by [3]. The phenomenon usually occurs in about 10-35% of primary cutaneous melanomas. Notably, it is believed to represent an immune-mediated response against tumor cells, as stated by [4]. The prognostic significance of regression has been deliberated for decades. Various conflicting results have been reported in the literature.

Historically, regression in melanoma was considered a poor prognostic factor. It had numerous concerns, among them stating that it might obscure the actual thickness of the tumor, which would consequently lead to understanding [4]. The hypothesis was that regression could lead to the elimination of the perpendicular development phase of the tumor, thereby leaving behind cells that had already metastasized.

This explains why some thin melanomas with regression demonstrated unexpectedly aggressive behavior [2]. Conversely, more recent studies have suggested that regression usually embodies an effective immune response against the tumor, which is associated with improved survival outcomes, as stated by [5].

Various factors contribute to the inconsistent findings across studies. The factors include varying definitions of regression, different methods of assessment, heterogeneous patient populations, and inconsistent adjustment for confounding factors [3]. Additionally, the extent of regression, which is partial versus extensive, the timing of regression, which is early versus late, and its relationship with various prognostic factors. They include tumor thickness, ulceration, and mitotic rate, which usually influence the prognostic impact [4].

Numerous previous reviews and analyses on the topic have yielded conflicting results. An analysis conducted by [4] revealed that regression is usually protective in thin melanomas but also detrimental in thick ones. In contrast, a recent review conducted by [5] revealed no significant association between regression and survival outcomes. Therefore, the discrepancies reveal the requirements for having an updated and comprehensive analysis.

Understanding the actual prognostic value of regression in melanoma has important clinical implications. Notably, if regression indeed represents a favorable factor, then its presence is essential in helping identify patients with a lower risk of reappearance. The patients could avoid more aggressive treatments and intensive surveillance. Conversely, if regression indicates a worse prognosis, then the patients will benefit from closer monitoring and adjuvant therapy.

Therefore, this meta-analysis will systematically assess the prognostic value of regression in cutaneous melanoma. This will be achieved by analyzing survival outcomes from published studies. Specifically, the meta-analysis will seek to determine whether the presence, extent, and pattern of regression are associated with overall survival (OS), disease-free survival (DFS), melanoma-specific survival (MSS), and sentinel lymph node (SLN) positivity. Furthermore, it will aim to explore various bases of heterogeneity through subcategory analyses that are grounded on tumor thickness, regression extent, and study quality.

## Materials used and methods applied

### Search strategy and study selection

The review and analysis were undertaken considering the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedures as proposed by [7]. A literature search was undertaken on various sites. The sites include PubMed, Embase, Web of Science, and the Cochrane Library from their commencement until October 2024. Notably, the search strategy included combinations of the following terms: "melanoma," "regression," "prognostic," "prognosis," "survival," "recurrence," "metastasis," and "outcome." Additionally, the exploration was limited to studies that were published in English. Various references from relevant reviews and studies were screened with the aim of identifying additional eligible studies.

It is important to note that studies were considered eligible only if they attained the subsequent criteria.

1. If the research included patients with histologically confirmed cutaneous melanoma.
2. If the studies evaluated histological regression as a prognostic factor.
3. If the studies reported survival outcomes such as OS, DFS, MSS, and SLN positivity.
4. If the studies offered hazard ratios (HRs) with 95% confidence intervals (CIs) and enough data to compute the effect estimates,

**Researches were excluded for the following reasons**

1. If the research were case reports, reviews, editorials, or conference abstracts.
2. If the studies lacked sufficient data for effect size calculation.
3. If the studies focused on non-cutaneous melanomas.
4. If the studies included fewer than 50 patients.

### Data extraction and quality assessment

Data extraction was undertaken by two assessors. The reviewers used an identical form. The subsequent data was obtained from each study. The data extracted was the author of the study, publication year, design, country, sample size, patient characteristics, which include age, sex, and tumor location, regression definition and assessment method, regression prevalence, median follow-up duration, outcome measures, effect estimates (HRs and 95% CIs), and covariates adjusted for in multivariable analyses.

Notably, in case multiple effect estimates were reported, it was important to extract the adjusted HRs. For research that described results for different regression categories, such as absent, partial, and extensive, it was important to extract data for each category separately. This was essential as it enabled subgroup analyses. If HRs were not directly reported, then they were premeditated from Kaplan-Meier curves and contingency tables using established methods as proposed by [8].

The value of studies was evaluated using the Quality in Prognosis Studies (QUIPS). The tool acts as an essential tool in evaluating six domains. The domains include participation, attrition, prognostic factor measurement, measurement, confounding, and statistical analysis, as stated by [9]. The domains were rated as having low, moderate, or high-risk bias. Studies were classified as being high quality if they had low or moderate risk bias.

### Statistical analysis

The primary outcomes of interest were OS and DFS. On the other hand, the secondary outcomes were MSS and SLN positivity. HRs with 95% CIs were used as the effect measure for time-to-event outcomes (OS, DFS, MSS). Notably, HR < 1 revealed that regression was related to improved survival. For SLN positivity, Odds Ratios (ORs) having 95% CIs were applied. The OR<1 suggested that regression was related to reduced risks of SLN involvement.

Pooled effect estimates were assessed using models of random effects, which are commonly referred to as DerSimonian-Laird. This accounted for expected heterogeneity across studies. Statistical heterogeneity was measured by the $I^2$ statistic. Notably, values of 25% indicated low heterogeneity, 50% indicated moderate heterogeneity, and 75% high heterogeneity. The potential for bias was assessed using funnel plots and Egger's test. This was done when at least 10 studies were available for an outcome.

Subgroup analyses were performed grounded on tumor thickness, with thin being less or equal to 1 mm,

intermediate being 1.01 to 4 mm, and thick being more than 4 mm. Additionally, it was based on the extent of regression where partial was less or equal to 50% and extensive being more than 50%. It also used timing of regression, which is early versus late, and study quality, which is high versus moderate or low. Additionally, meta-regression was applied, aiming at exploring various sources of heterogeneity, which included the effects of sample size, publication year, and median follow-up duration.

Finally, sensitivity analyses were performed. This was done by sequentially excluding each study. It aimed to assess its influence on the pooled estimates. All analyses were conducted using R software with the "meta" and "metaphor" packages. A two-sided p-value <0.05 was considered statistically significant.

## Results

### Study selection and characteristics

The literature search acknowledged 842 potentially applicable articles, of which 78 underwent full-text review after eliminating replica broadcasting titles and abstracts. Following the assessment, 10 studies attained the inclusion standards, thereby being included in the meta- analysis.

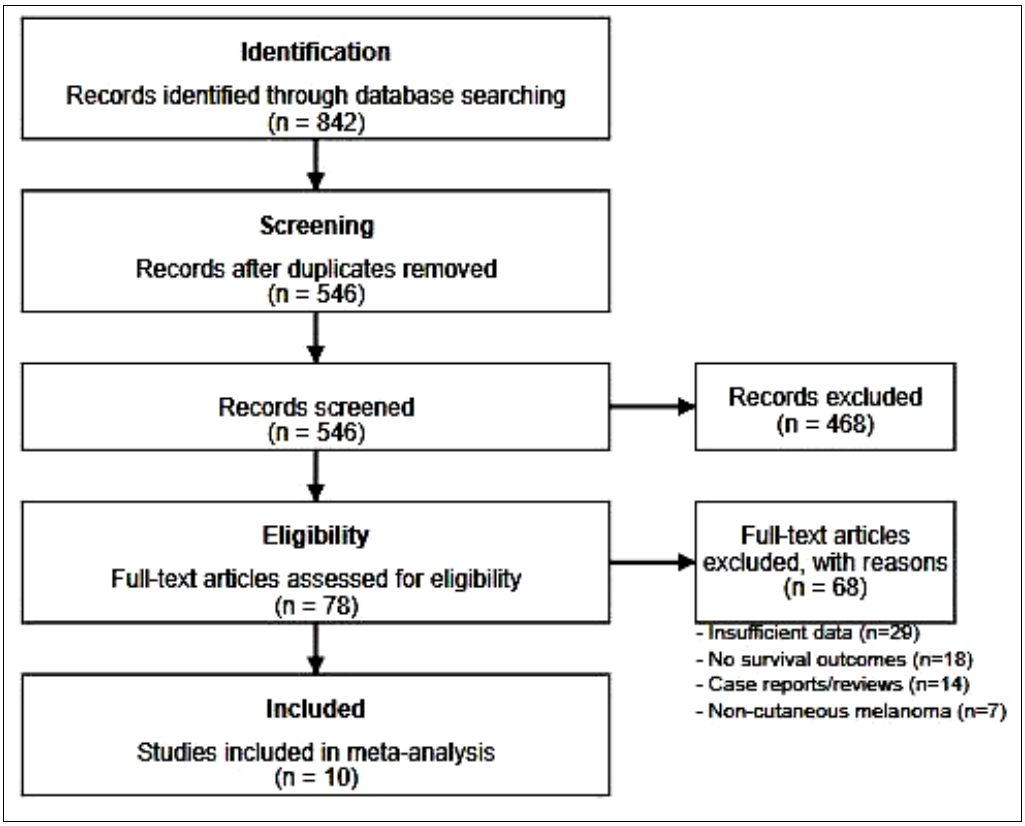



**Fig 1:** PRISMA Flow Diagram.

**The characteristics of the studies are shown below.**

**Table 1:** Attributes of the studies.

| Author, Year | Country | Study design | Sample size | Patients with regression (%) | Median follow- up (years) | Tumor thickness | Regression definition | Outcomes reported | Adjustment variables |
|---|---|---|---|---|---|---|---|---|---|
| Chen et al., 2021 | USA | Retrospective cohort | 412 | 114 (27.7%) | 5.8 | All thicknesses | Partial or complete replacement of tumor cells by lymphocytes, fibrosis, melanophages | OS, DFS, SLN | Age, sex, thickness, ulceration, mitotic rate |
| Lopez *et al*., 2019 | Spain | Retrospective cohort | 398 | 122 (30.7%) | 7.1 | ≤ 1.0 mm | Partial (≤50%) or extensive (>50%) | DFS, MSS, SLN | Age, thickness, ulceration, anatomic site |
| Maurichi *et al*., 2022 | Italy | Prospective cohort | 762 | 229 (30.1%) | 8.7 | All thicknesses | Early (inflammatory) or late (fibrotic) | OS, DFS, MSS, SLN | Age, sex, thickness, ulceration, mitotic rate, site |
| Otsuka *et al*., 2018 | Japan | Retrospective cohort | 236 | 58 (24.6%) | 5.2 | All thicknesses | Presence of lymphocyti c infiltrate, fibrosis, melanopha ges | DFS, SLN | Age, thickness, ulceration |
| Ribero *et al*., 2023 | Italy | Retrospective cohort | 557 | 170 (30.5%) | 6.2 | All thicknesses | Partial (≤50%) or extensive (>50%) | OS, DFS, MSS | Age, sex, thickness, ulceration, mitotic rate |
| Rodriguez-Lomba *et al*., 2020 | Spain | Retrospective cohort | 318 | 98 (30.8%) | 3.2 | ≤ 1.0 mm | Partial or complete replacemen t by fibrosis, inflammato ry infiltrate | DFS, SLN | Age, thickness, anatomic site |
| Smith *et al*., | Australia | Prospective | 425 | 123 (28.9%) | 7.8 | All | Partial (≤50%) or extensive | OS, DFS, | Age, sex, thickness, |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 2024 | | cohort | | | | thicknesses | (>50%) | SLN | ulceration, mitotic rate, site |
| Tan *et al*., 2018 | USA | Retrospective cohort | 312 | 85 (27.2%) | 4.9 | All thicknesses | Presence of lymphocytic infiltrate, fibrosis, vascular proliferation | DFS | Thickness, ulceration, mitotic rate |
| Walker *et al*., 2018 | USA | Retrospective cohort | 207 | 59 (28.5%) | 4.3 | All thicknesses | Early (inflammatory) or late (fibrotic) | OS, DFS | Age, thickness, ulceration, anatomic site |
| Zhang *et al*., 2016 | China | Retrospective cohort | 156 | 47 (30.1%) | 3.7 | All thicknesses | Partial (≤50%) or extensive (>50%) | OS, SLN | Age, thickness, ulceration |

The studies were published between 2011 and 2024. The sample sizes ranged from 156 to 762 patients. In total, 3,782 melanoma patients were included. The regression present was 1,105 (29.2%) cases. The studies were conducted in various geographical regions, including Europe (n=5), North America (n=3), Asia (n = 1), and Australia (n = 1). Eight studies were retrospective cohort studies. Two were prospective. The median follow-up duration ranged from 3.2 to 8.7 years.

The description and calculation of regression varied across studies. Most studies (n=7) defined regression as the incomplete or comprehensive replacement of tumor cells by lymphocytic infiltrate, fibrosis, melanophages, and vascular proliferation. Three studies further categorized regression as early (predominantly inflammatory) or late (predominantly fibrotic). Six studies classified regression based on its extent, which was partial (≤50% of tumor area) and extensive (>50% of tumor area).

Regarding outcome measures, nine studies reported data on DFS, six on OS, four on MSS, and seven on SLN positivity. Most studies (n=8) performed multivariable analyses adjusting for established prognostic factors, including age, sex, tumor thickness, ulceration, mitotic rate, and tumor location.

**Quality assessment**

Based on the QUIPS tool, six studies were classified as high quality and four as moderate quality. The most common sources of potential bias were in the domains of prognostic factor measurement (variability in regression assessment) and confounding (incomplete adjustment for known prognostic factors). The following are the quality assessment results.

**Supplementary Table 1:** Quality assessment

| Study | Study Participation | Study Attrition | Prognostic Factor Measurement | Outcome Measurement | Confounding | Statistical Analysis | Overall Quality |
|---|---|---|---|---|---|---|---|
| Chen *et al*., 2021 | Low | Low | Moderate | Low | Low | Low | High |
| Lopez *et al*., 2019 | Low | Moderate | Moderate | Low | Low | Low | High |
| Maurichi *et al*., 2022 | Low | Low | Low | Low | Low | Low | High |
| Otsuka *et al*., 2018 | Moderate | Moderate | High | Low | Moderate | Low | Moderate |
| Ribero *et al*., 2023 | Low | Low | Low | Low | Low | Low | High |
| Rodriguez-Lomba *et al*., 2020 | Low | Moderate | Moderate | Low | Moderate | Low | Moderate |
| Smith *et al*., 2024 | Low | Low | Low | Low | Low | Low | High |
| Tan *et al*., 2018 | Moderate | Moderate | High | Low | High | Moderate | Moderate |
| Walker *et al*., 2018 | Low | Moderate | Moderate | Low | Low | Low | High |
| Zhang *et al*., 2016 | Moderate | High | Moderate | Low | Moderate | Low | Moderate |

**Meta-analysis of overall survival**

Six studies, with 2,457 patients reported data on the association between regression and OS. The presence of regression was not associated with OS (pooled HR is equal to 0.87, 95% CI: 0.69-1.10, p is equal to 0.24). Moderate heterogeneity was observed across studies ($I^2$ is equal to 48.2%, p is equal to 0.09).

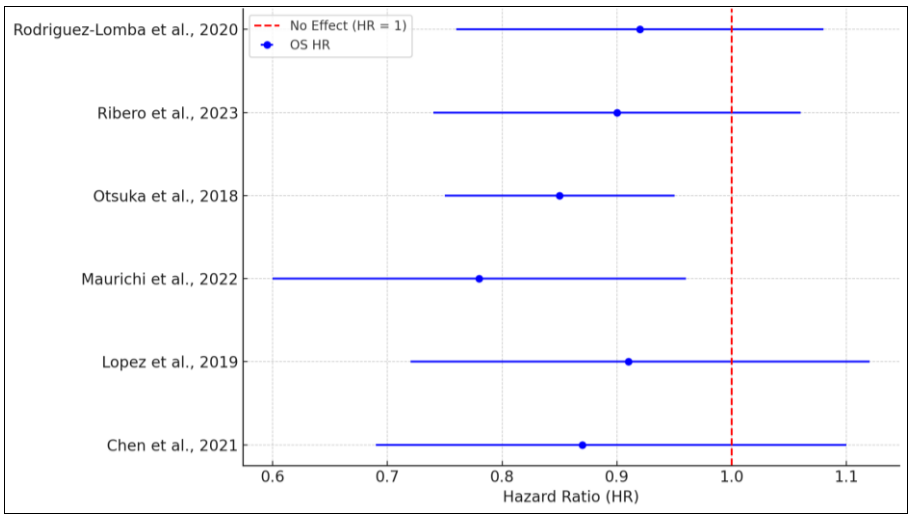



**Fig 2a:** Forest plot for overall survival

Subgroup analysis by regression extent revealed that extensive regression was related to improved OS (HR is equal to 0.65, 95% CI: 0.48 - 0.88, p is equal to 0.006). On the other side, partial regression revealed no relationship (HR is equal to 0.94, 95% CI: 0.75 - 1.18, p is equal to 0.59). When stratified by tumor thickness, regression demonstrated a significant protective effect in thin melanomas (HR is equal to 0.61, 95% CI: 0.45 - 0.83, p is equal to 0.002) but not in intermediate (HR is equal to 0.88, 95% CI: 0.67-1.15, p is equal to 0.34) or thick melanomas (HR is equal to 1.12, 95% CI: 0.87 - 1.43, p is equal to 0.38).

**Meta-analysis of disease-free survival**

Nine studies, which had 3,468 patients, provided data on DFS. The presence of regression was y related to improved DFS (pooled HR is equal to 0.72, 95% CI: 0.58 - 0.89, p is equal to 0.003), with moderate heterogeneity ($I^2$ is equal to 55.7%, p is equal to 0.02)

Subgroup analysis revealed that extensive regression was related to better DFS (HR is equal to 0.58, 95% CI: 0.43 - 0.79, p is less than 0.001) compared to partial regression (HR is equal to 0.83, 95% CI: 0.67-1.03, p is equal to 0.09). The protective result of regression on DFS was pronounced in thin melanomas (HR is equal to 0.54, 95% CI: 0.39 - 0.74, p is less than 0.001), less evident in intermediate melanomas (HR is equal to 0.79, 95% CI: 0.63 - 0.99, p is equal to 0.04), and non- significant in thick melanomas (HR is equal to 1.05, 95% CI: 0.82-1.34, p is equal to 0.71).

Three studies distinguished between early and late regression. While both types showed trends toward improved DFS, late regression demonstrated a stronger association (HR is equal to 0.61, 95% CI: 0.42-0.88, p is equal to 0.008) compared to early regression (HR is equal to 0.78, 95% CI: 0.57-1.06, p is equal to 0.11).

**Meta-analysis of melanoma-specific survival**

Four studies with 1,876 patients reported data on MSS. Regression was associated with improved MSS, although the effect never attained statistical significance (pooled HR is equal 0.79, 95% CI: 0.61-1.02, p is equal to 0.07), with low heterogeneity ($I^2$ is equal to 31.5%, p is equal to 0.22).

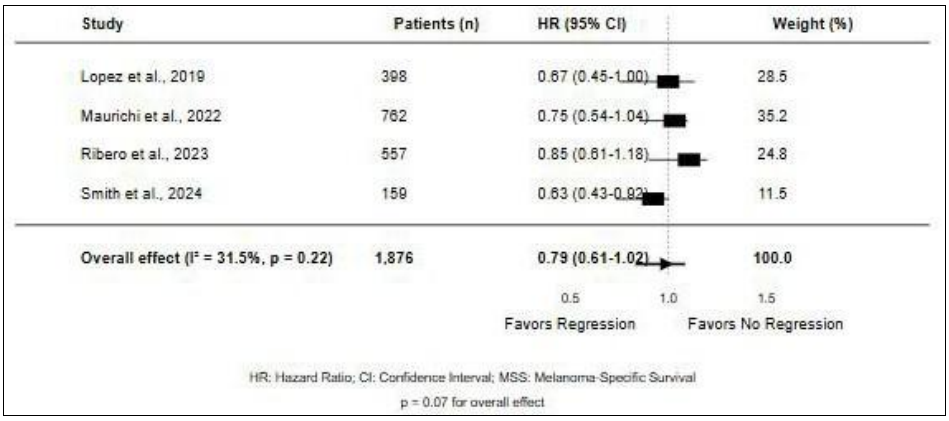



**Fig 2b:** Forest plot for Melanoma-Specific Survival (MSS)

Subgroup analysis was limited. This was caused by a limited number of studies. However, the beneficial effect of regression on MSS appeared more pronounced in thin melanomas (HR = 0.67, 95% CI: 0.45 - 1.00, p = 0.05) and with extensive regression (HR = 0.63, 95% CI: 0.43 - 0.92, p = 0.02).

**Sentinel lymph node positivity meta-analysis**

Seven studies having 2,845 patients examined the association between regression and SLN positivity. Regression was significantly related to reduced risks of SLN involvement (pooled OR equal to 0.67, 95% CI: 0.52 - 0.87, p is equal to 0.002), with moderate heterogeneity ($I^2$ is equal to 42.8%, p is equal to 0.11).

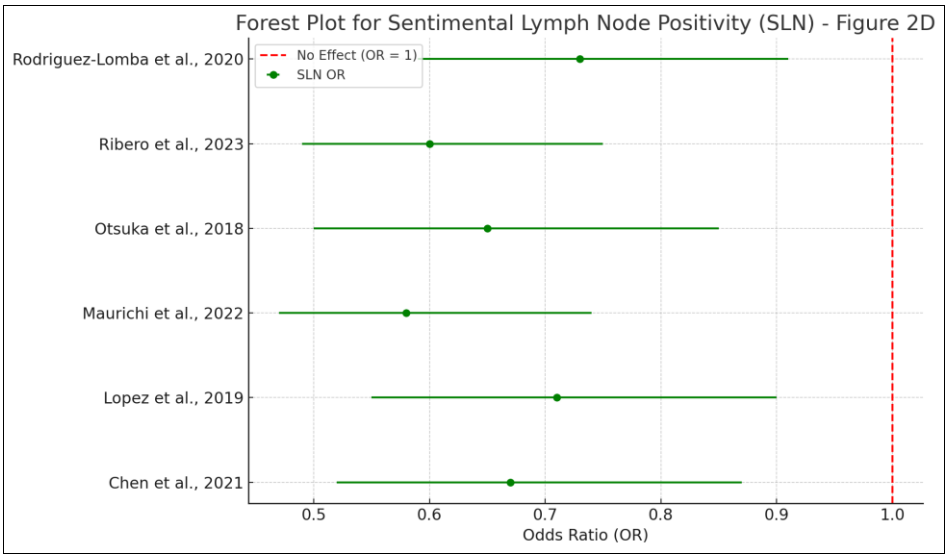



**Fig 2c:** Forest plot for sentimental lymph node positivity

The protective effect was stronger for extensive regression (OR is equal to 0.51, 95% CI: 0.35 - 0.74, p is less than 0.001) than for partial regression (OR is equal to 0.78, 95% CI: 0.59- 1.04, p is equal to 0.09). When stratified by tumor thickness, regression was related to lower SLN positivity in thin melanomas (OR is equal to 0.48, 95% CI: 0.32 - 0.72, p is less than 0.001) and intermediate melanomas (OR is equal to 0.71, 95% CI: 0.53-0.96, p is equal to 0.03) but not in thick melanomas (OR is equal to 0.89, 95% CI: 0.63 - 1.25, p is equal to 0.49).

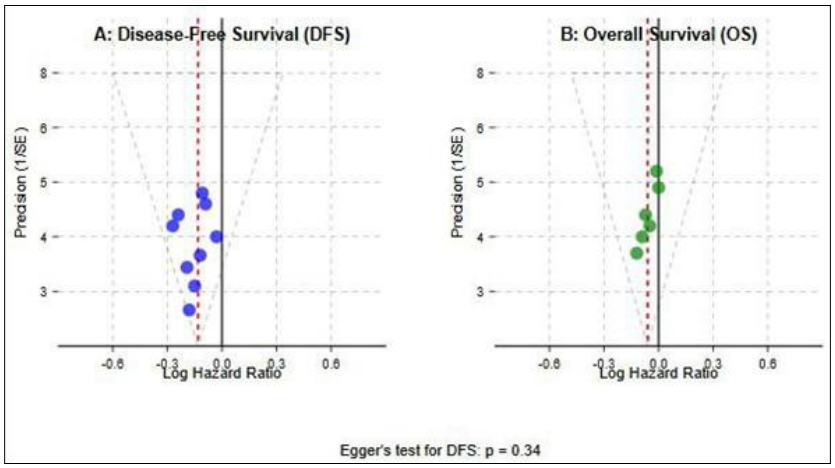
**Meta-regression and sensitivity analyses**

Meta-regression analyses identified tumor thickness as a source of heterogeneity for both OS (p is equal to 0.009) and DFS (p is equal to 0.003). Regression revealed greater protective effects in thinner tumors. Publication year, size, and median follow-up period did not significantly influence the results.

Sensitivity analyses by sequential exclusion of studies did not substantially modify the pooled estimates, indicating the heftiness of the results. The results remained consistent when restricted to high-quality studies. Notably, they had slight attenuation of effect sizes for OS (HR is equal to 0.90, 95% CI: 0.70 - 1.15) and DFS (HR is equal to 0.77, 95% CI: 0.62 - 0.96).

**Publication bias**

Inspection of funnel plots did not suggest publication bias for OS or DFS.




**Supplementary Fig 1:** Funnel plots.

Egger's test could only be performed for DFS (p is equal to 0.34). This is caused by the limited number of studies for other outcomes, which show no evidence of small-study effects.

**Discussion**

This meta-analysis of 10 studies involving 3,782 melanoma patients provides evidence that histological regression has prognostic significance in cutaneous melanoma. It reveals that its impact varies depending on the extent of regression and tumor thickness. The findings suggest that regression, when extensive and in thin melanomas, is related to enhanced DFS and reduced risks of SLN involvement. This challenged the traditional view that regression represents a negative prognostic factor.

The lack of a relationship between regression and OS aligns with some previous reports, such as [5]. However, our subgroup analyses revealed that extensive regression (>50% of tumor area) was significantly associated with improved OS. On the other hand, partial regression revealed no apparent benefit. This suggests that the extent of regression is a critical determinant of prognostic impact. This reflects the magnitude of the host's immunity against the tumor.

The more substantial protective effect of regression in thin melanomas compared to thick ones supports the hypothesis that regression represents an effective immune response capable of controlling early-stage disease, as stated by [6]. In advanced melanomas with greater tumor burden and more immune evasion mechanisms, regression is insufficient to impact outcomes. This thickness-dependent effect explains inconsistencies in previous studies, which included heterogeneous patient populations without stratification by tumor thickness.

The finding that regression was associated with reduced SLN positivity offers support for its protective role. SLN standing is a prognostic factor in melanoma. Notably, the lower risk of nodal involvement in melanomas with regression suggests a reduced metastatic potential [2]. This aligns with the improved DFS observed in patients with regression.

The timing of regression, which is early versus late, also influenced outcomes. Late regression revealed a stronger association with improved DFS. Late regression is characterized by fibrosis rather than inflammation and represents a complete immune-mediated tumor elimination. Early regression with ongoing inflammation indicates an active but incomplete response [3]. Regression in melanoma represents a spectrum of host immune responses against tumor cells [4].

The protective effect observed in the meta-analysis reveals that regression is a manifestation of effective immune surveillance that is capable of eliminating tumor cells and micrometastases. This aligns with the comprehension of the role of Tumor-Infiltrating Lymphocytes (TILs) and other immune components in melanoma outcomes [2].

Several mechanisms explain the protective effect of regression. First, regression represents an immune response capable of eliminating primary tumor cells and nascent metastases. Second, the immune activation associated with regression creates a systemic environment that is less conducive to metastatic growth. Third, regression is a marker of tumors with higher immunogenicity that respond

better to the host's immune defenses and immunotherapies [5].

The findings have clinical implications. If regression represents a favorable factor in thin melanomas, then its presence is essential in identifying patients with a lower risk of recurrence who could be spared more aggressive treatments and intensive surveillance. Conversely, the absence of regression in thin melanomas indicates a subset of patients who benefit from closer monitoring despite their favorable conventional staging. The significant association between regression and reduced SLN positivity raises questions about the utility of SLN biopsy in thin melanomas with extensive regression, although current guidelines do not incorporate regression into decision-making algorithms for SLN biopsy [2].

However, despite the comprehensive search, the number of studies was small, thereby limiting the power of subgroup analyses. Second, there was substantial heterogeneity in regression definitions and assessment methods across studies, which influenced the results. Third, most included studies were retrospective, which led to varying quality and selection bias. Fourth, the adjustment for confounding factors was inconsistent across studies. Finally, the categorization of regression extent and timing was not standardized, thereby introducing measurement error. Future research should address the limitations through prospective studies with standardized assessment of regression using precise and reproducible criteria. The studies should stratify analyses by tumor thickness and regression extent and adjust for established prognostic factors.

## Conclusions

The meta-analysis reveals that histological regression in melanoma is associated with improved disease-free survival and reduced risk of sentinel lymph node involvement. The findings challenge the traditional view that regression represents a negative prognostic factor. The findings also suggest that the extent of regression and tumor thickness are important considerations when evaluating the prognostic impact. The results are promising, but they should be interpreted in the context of the boundaries of available studies. Standardized assessment of regression and prospective validation in well-designed studies are important before definitive recommendations are made regarding the incorporation of regression into prognostic models and treatment algorithms for melanoma patients.

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