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## **Prognostic role of Histologic regression in primary cutaneous melanoma:**

### **A Systematic Review and Meta-analysis**

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## WHAT'S ALREADY KNOWN?

The prognostic significance of histological regression in primary melanoma has been debated for many years. Still, no robust data is reported on the prognostic value of histological regression.

## WHAT DOES IT ADD?

The results of this meta-analysis may be useful when looking at the histological regression in a melanoma to consider it as a favourable prognostic factor, probably linked to early activation of the host immune system against the tumour.

## ABSTRACT

**INTRODUCTION** The prognostic significance of histological regression in primary melanoma has been debated for many years. We aim to review the evidence to look how histological regression may affect prognosis.

**METHODS.** A systematic review was performed by searching in MEDLINE, Scopus, and the Cochrane Library from January 1st 1966, through August 1st 2015. All studies that reported HR or data on survival and histological regression were included.

Primary random-effects meta-analyses were used to summarise outcome measures.

Heterogeneity was assessed using the  $\chi^2$  test and I<sup>2</sup> statistic. To assess the potential bias of small studies we used funnel plots and the Begg and Mazumdar adjusted rank correlation method.

Summary of survival outcomes were measured as Hazard Risks or Relative risk of death at 5 years according to the presence of histological regression of primary melanoma.

**RESULTS** 183 articles were reviewed out of 1876. 10 studies comprising 8557 patients were included. Patients with histological regression had a lower Relative Risk of death ( 0.772;95%CI,

0.612-0.973) than patients without. Examination of the funnel plot did not provide evidence of publication bias.

**CONCLUSION** The results showed that histological regression is a protective factor for survival.

## **INTRODUCTION**

Histological regression in melanoma has been defined as an area within the tumour in which neoplastic cells have disappeared or become reduced in number from the dermis (and occasionally from the epidermis) and have been substituted by fibrosis. This phenomenon is accompanied by melanophagia, new vessels and a variable inflammatory infiltrate [1,2,3]. The frequency of histological regression is variable in literature, but it has been reported from 10% to 35% [4].

Meanwhile, the prognostic significance of histological regression in primary melanoma has been debated for many years. Some studies reported potential poor prognosis in association with histological regression because the disappearance of a portion of the tumour may lead to an underestimation of the original Breslow thickness. Its prognostic value has often been analysed, although no accordance is reported in literature. Although often debated, histological regression never reached the status of a prognostic criterion for melanoma staging classification.

Some studies have reported an increasing risk of developing a metastasis and consequently a poorer survival rate [5,6] for patients with histological regression of primary melanoma.

Contrarily, other studies have shown that histological regression does not increase the risk of metastases [1,7] and does not negatively impact prognosis[8].

The most important prognostic factor in intermediate and thick melanoma is sentinel lymph node positivity [9,10]. A recent meta-analysis on 10098 patients looking at the association between SLN status and histological regression have showed a lower risk of SLN metastasis in patients carrying this feature in their tumour (OR=0.56; 95%CI: 0.41-0.77)[11]. Results reported in literature on the survival role of histological regression are usually based on monocentric case series and are not conclusive on the significant role of histological regression.

To review the evidence that histological regression may affect survival, we conducted a meta-analysis of published literature to provide a more objective estimate of the mortality risk in patients with histological regression in primary melanoma tumours.

## **MATERIALS AND METHODS**

We carried out this review in accordance with PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis guidelines) [12].

### **Search Strategy, Eligibility Criteria and Study Selection**

A systematic review of original articles and abstracts analysing the survival of patients with histological regression of primary melanoma was performed by searching in MEDLINE, Scopus and Cochrane Library from January 1<sup>st</sup> 1966 till July the 1<sup>st</sup> 2015. The search strategy included the following keywords in various combinations: “melanoma,” “regression,” “histological regression”, “survival”, and “prognosis”; 1876 citations were reported in total. In addition, we reviewed articles and relevant reviews to locate publications missed by the database searches. Two authors (SR and EM) independently assessed the eligibility of studies. Any disagreement

was settled by consensus, including a third and fourth investigator (EF and SOA). The article titles and abstracts were used for initial screening, followed by review of the full text. There was no restriction criterion on the number of patients enrolled in the study. Only original manuscripts in English language were included. Searches were supplemented by scanning bibliographies of included articles. We excluded articles that reported no data, such as review articles and editorials. If duplicate data were present in separate publications, we included the publication with the larger amount of data or the more recent. All articles that reported survival data regarding histological regression in melanoma patients were eligible for inclusion.

### **Data Extraction**

We used a data extraction form based on the Cochrane consumers and communication review group data examination template [13]. For each study selected, the following data were extracted: journal, year, study design, number of patients, age, gender, melanoma thickness, ulceration, and histological regression. The survival data were considered as survival rate at 5 years or HR. As studies reported different types of measurements we performed a sensitivity analysis, in accordance with the current literature [14].

### **Statistical analysis**

To integrate previous findings on this topic, we performed a meta-analysis of published literature to provide an estimation of the risk of death in melanoma patients with evidence of histological regression in the primary tumour. Because studies were found to be heterogeneous ( $I^2 > 30\%$ ), summary Rate Ratios (RRs) with corresponding 95% confidence intervals (95% CIs) were calculated using random-effects modelling. Publication bias was assessed through the

construction of a funnel plot for the primary endpoint, as well as with the Begg and Mazumdar adjusted rank correlation method and Egger test.

Statistical analyses were performed using the Stata 13.0 statistical software (StataCorp, College Station, TX, U.S.A.).

## **RESULTS**

### **Characteristics of Included Studies**

The initial search resulted in 1876 citations (Figure 1). The title and abstract of each retrieved publication was reviewed to confirm that the article included survival data regarding histological regression melanoma tumours. In the event that this approach was not informative, the full article was retrieved and further reviewed. This process resulted in the selection of 183 studies. Of these, 173 were eventually excluded from this analysis because they did not show clear results on survival and histological regression. In particular, it was not possible to differentiate the survival analyses (in terms of HR or survival rate) according to histological regression. 17 studies reported overlapping data points from other studies were also excluded. Therefore, ten studies [15-24] were eligible to be included in the systematic review and meta-analysis. Three of them reported data pooled from many centres (Table 1) [16, 21, 22].

In the study, 8557 patients were finally included. Survival data were described as HR in 4 studies [18,22,23,24]. Survival rate at 5 years was reported in 6 studies [15-17, 19-21]. Meanwhile, histological description of regression was reported in 9 papers [15-23]. In 3 studies, the presence of histological regression was significantly associated to a better prognosis [18, 20, 22], while in 7 it was not significantly associated to survival [15-18,20,22,24]. All studies reported clinical data of the patients on gender and age. Among them, data on Breslow thickness, which is the major prognostic factor in melanoma patients, were described as mean depth in 2 studies [16, 23]



or as median in 1 [20]. In the remaining 7 studies [15,17-19,21,22,24], Breslow thickness was reported as categorical cut-off. Ulceration distribution was described in 8 out of 10 studies [15, 18-24].

### **Outcome of Meta-analysis**

In the 10 studies included, patients with histological regression of primary melanoma had a lower likelihood of death (RR 0.772; 95% CI, 0.612-0.973) than patients without histological regression (Figure 2). Examination of the funnel plot (Figure 4) did not provide evidence of publication bias. Similarly, there was no evidence of such bias for the sensitivity analysis. In fact, it displays that the points are evenly distributed and symmetrical, thus showing absence of asymmetry and that the results of the study are reliable. This evidence was confirmed by the results of the Begg and Mazumdar test (p-value 0.37) and Egger test (p-value=0.19). When stratified on the main outcome of the studies, the meta-analysis of those reporting RR at 5 years was still significant (RR 0.722; CI, 0.535-0.975) (Supplementary figure 1), while the one of those reporting HR was not (HR 0.852; CI, 0.575-1.263) (Supplementary figure 2).

Examination of the funnel plot (Supplementary Figure 3 and Supplementary Figure 4) did not provide evidence of publication bias

### **DISCUSSION**

In this systematic review and meta-analysis including 10 studies [15-24] and more than 8500 patients, we found that histological regression is a protective feature for survival in melanoma patients: melanoma patients with regression had a lower likelihood to die (RR 0.772; 95% CI, 0.612-0.973) than patients without histological regression.

### **Clinical significance**

Reported data regarding the prognostic role of histological regression has hitherto been conflicting [5,25-27]. In the past, histological regression has traditionally been considered as a marker of poor prognosis, because it leads to an under-estimation of melanoma thickness [5]. Some studies found that histological regression in melanoma does not increase the risk of lymphatic metastasis therefore do not affect prognosis, while others studies reported that it is associated with a poor prognosis, particularly in thin melanomas [25,26]. A recent paper on a large setting of stage I-II patients has shown a protective role on prognosis in melanoma patients with histological regression(stage I-II AJCC ) [23]. At the same time, the discussion regarding the SLN performance in thin melanoma with regression has arrived to an answer [28]: a meta-analysis has confirmed that histological regression is not a criterion for recommendation of SLNB in thin melanomas [12].

To our knowledge, the current report represents the first meta-analysis to focus on the prognostic value of histological regression in melanoma patients. The majority of the studies were not able to define the histological regression as protective or worsening in survival. In particular, there is no paper included in the study that reported a significantly negative association between histological regression and survival (See fig 2). We have performed this meta-analysis to determine if pooling data together would allow us to achieve a final consideration. We found that the risk of death was significantly lower in patients with histological regression in melanoma tumours compared to those without.

No robust data are reported on the prognostic value of histological regression. So far, the biological role of histological regression in primary melanoma has been interpreted in a contradictory fashion. Once histological regression has been was considered able to decrease the

tumour thickness, leading to a sub-staging of the Breslow thickness. On the other hand, Tumour regression has been described as an indicator of a tumour-directed immune response[3]. Tumour-directed T-cell responses, however, may contribute to an improved prognosis as shown by the successful treatment with drugs stimulating the immune system's responsiveness [29-33].

As melanoma is a strong immunogenic tumour, a strong host immunological response to the tumour is thought to be the cause of the histological regression of the primary tumour. It would therefore be expected that the presence of regression would confer survival advantage.

Nevertheless, it can be suggested that a host immunological response to the tumour could be the basis of regression. Further, histological regression could mirror the power of the immunologic system against the primary tumour and its presence should be considered prognostically favourable. Ma *et al.* [34] showed that histological regression results from a T-cell immune response associated with a decreased risk of nodal progression. In particular, the same authors described a down-regulation of the anti-tumour immunity in the positive SLN with an increase in regulatory T cells, compared with the negative non-sentinel node from the same nodal basin.

## **Limitations**

Significant heterogeneity with respect to quality characteristics has been present among the studies, as confirmed by the Q statistics. The authors are conscious of heterogeneity in this study in terms of melanoma features (ulceration and thickness). All the included studies described melanoma cohorts as classically reported in literature and the large majority of them included both thin and thick melanomas, considering consecutive case series of patients. As suggested by the scientific literature [35], meta-analysis in the presence of heterogeneity is commonly performed

by using a random-effects model, thus we have chosen to use this statistical model to solve this concern.

Furthermore, because covariance information was not consistently reported in the published studies, we could not adjust our pooled estimate for the confounding effects of formal meta-regression. Thus, the reliability of summary estimates is contingent upon the quality of the studies pooled. Although included studies met many of the a priori quality metrics, important deficiencies remained.

Another limitation that has to be acknowledged is the use of combined rate ratios, which we calculated from the data extracted from the selected studies. Further, due to the fact that we combined different types of measurements, methodological concerns may arise, leading to potential bias [14,36].

Another potential limitation is that the included studies may have had different definitions of histological regression. As the definition of this feature is sometimes defined from a pathological point of view, the subjectivity of pathology could influence the final report of each melanoma. Despite this, the modality of evaluation of histological regression has been described in the same modality in 9 papers out of 10: only Ito and colleagues [24] did not describe how histological regression was evaluated. Indeed, we cannot guarantee the quality of superimposable data. In line with International Consensus guidance, further studies are encouraged to utilise more reproducible evaluation features of histological regression, such as the percentage of the lesion regressed (etg. 50%)[25]. Moreover, this study is limited by the fact that it included only observational studies. Most studies were retrospective from a single institution. Pitfalls in dermatopathology are always possible, but this is a common problem of all retrospective studies in which there is not a central control. In some cases, multiple reports were published overtime from the same institution and

considerable effort was expended in an attempt to identify and utilise the most suitable report. It is possible, however, that some patients were not included when trying to avoid duplicates in consecutive studies reported by the same group. Nevertheless, based on the size of the study, it is unlikely that missing these cases would have significantly affected the results. These limitations underscore the need for standardised reporting of relevant covariates in future observational studies. From a methodological perspective, histological regression needs a worldwide consensus regarding its definition in order to further analyse this intriguing feature. All other prognostic factors should also be collected accurately. It has also been recommended that two pathologist separately assess the histological regression in primary melanoma specimens and that a high inter-observer agreement is achieved.

## **Conclusion**

The results of this meta-analysis may be useful when looking at the histological regression in a melanoma to consider it as a favourable prognostic factor, probably linked to early activation of the host immune system against the tumour.

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Figures are available on line

FIGURE TITLE:

Figure 1. Flowchart of Article Search and Inclusion

Figure 2. Likelihood of death in Patients With Melanoma with regression

Figure 3: Funnel Plot of the Studies Included in the Meta-analysis

Figure 1 supplementary : Likelihood of death in Patients With Melanoma with regression (data reported RR)

Figure 2 supplementary Likelihood of death in Patients With Melanoma with regression (data reported HR)

Figure 3 supplementary Funnel Plot of the Studies Included in the Meta-analysis (data reported RR)

Figure 4 supplementary Funnel Plot of the Studies Included in the Meta-analysis (data reported HR)

FIGURE LEGEND:

Figure 2: Illustrated are the standardized Relative risk of death for the studies included in the meta-analysis. Patients with histologic regression of primary melanoma had a lower likelihood of death (RR 0.772; 95% CI, 0.612-0.973); darker dashed vertical line) than patients without regression.

Figure 3: The funnel plot displays points (each representing an included study) that are evenly and symmetrically distributed, thus showing the absence of study bias and suggesting that the results of the studies are reliable.