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# Prognostic role of histological regression in primary cutaneous melanoma: a systematic review and meta-analysis

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## Summary

The prognostic significance of histological regression in primary melanoma has been debated for many years. We aim to review the evidence to see how histological regression may affect prognosis. A systematic review was performed by searching in MEDLINE, Scopus and the Cochrane Library from 1 January 1966 to 1 August 2015. All studies reporting hazard ratios or data on survival and histological regression were included. Primary random-effects meta-analyses were used to summarize outcome measures. Heterogeneity was assessed using the $\chi^2$-test and $I^2$-statistic. To assess the potential bias of small studies we used funnel plots and the Begg and Mazumdar adjusted rank correlation method. Summaries of survival outcomes were measured as hazard ratios or relative risk of death at 5 years according to the presence of histological regression of primary melanoma. In total, 183 articles were reviewed out of 1876 retrieved. Ten studies comprising 8557 patients were included. Patients with histological regression had a lower relative risk of death (0·77, 95% confidence interval 0·61–0·97) than those without. Examination of the funnel plot did not provide evidence of publication bias. The results showed that histological regression is a protective factor for survival.

### What's already known about this topic?

- The prognostic significance of histological regression in primary melanoma has been debated for many years.
- No robust data are reported on the prognostic value of histological regression.

### What does this study add?

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

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.[1–3] The frequency of histological regression is variable in the literature, but values from 10% to 35% have been reported.[4]

The prognostic significance of histological regression in primary melanoma has been debated for many years. Some

studies have reported a 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 association is reported in the literature. Although often debated, histological regression has never obtained 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 (SLN) positivity.[9,10] A recent meta-analysis on 10 098 patients looking at the association between SLN status and histological regression showed a lower risk of SLN metastasis in patients having this feature in their tumour [odds ratio 0·56, 95% confidence interval (CI) 0·41–0·77].[11] Results reported in the 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 the 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 the Cochrane Library from 1 January 1966 to 1 August 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 (S.R. and E.M.) independently assessed the eligibility of studies. Any disagreement was settled by consensus, including a third and fourth investigator (E.F. and S.O.A.).

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 were included. Searches were supplemented by scanning the bibliographies of the 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 reporting survival data regarding histological regression in patients with melanoma were eligible for inclusion.

### Data extraction

We used a data extraction form based on the Cochrane Consumer 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, sex, melanoma thickness, ulceration and histological regression. The survival data were considered as survival rate at 5 years or hazard ratio (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 estimate of the risk of death in patients with melanoma with evidence of histological regression in the primary tumour. As the studies were found to be heterogeneous ($I^2 > 30\%$), summary rate ratios (RRs) with corresponding 95% CIs were calculated using random-effects modelling. Publication bias was assessed through the construction of a funnel plot for the primary end point, as well as with the Begg and Mazumdar adjusted rank correlation method and Egger test. Statistical analyses were performed using Stata 13.0 statistical software (StataCorp, College Station, TX, U.S.A.).

## Results

### Characteristics of the included studies

The initial search resulted in 1876 citations (Fig. 1). The title and abstract of each retrieved publication were reviewed to confirm that the article included survival data regarding histological regression in 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. Seventeen studies reporting overlapping data points from other studies were also excluded. Therefore, 10 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).[18,21,22]

In this review, 8557 patients were finally included. Survival data were described as the HR in four studies.[18,22–24] Survival rate at 5 years was reported in six studies.[15–17,19–21]

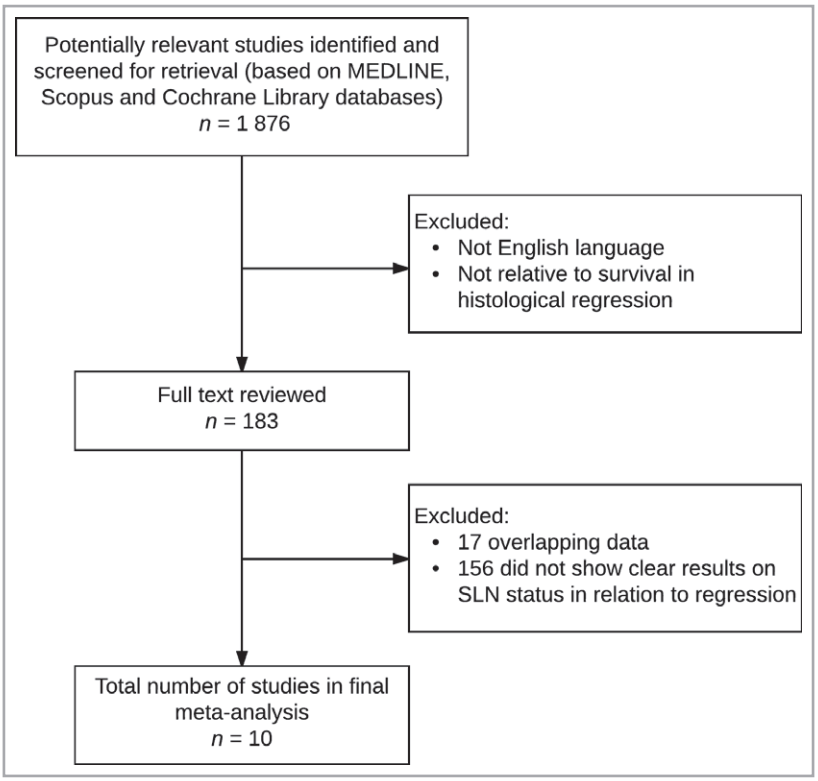


**Fig 1.** Flowchart of article search and inclusion. SLN, sentinel lymph node.

**Table 1** Characteristics of the included studies

| | | | | Regression | | Survival data | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 5-year survival rate | | |
| Study | Region | Sample size | Centre | Yes | No | Breslow thickness | Regression | Not regression | HR (95% CI) |
| Johnson 1985[15] | U.S.A. | 261 | Monocentric | 32 | 229 | Thin and thick | 62% | 50% | – |
| Kelly 1985[16] | U.S.A. | 841 | Monocentric | 173 | 668 | < 0·76 mm | 91·8% | 97·8% | – |
| | | | | | | 0·76–1·5 mm | 70·9% | 71·6% | |
| | | | | | | > 1·5 mm | 53·6% | 57·4% | |
| Clemente 1996[17] | Italy | 285 | Monocentric | 37 | 248 | Thin and thick | 57% | 49% | – |
| Måsbäck 1997[18] | Sweden | 461 | Monocentric | 268 | 193 | Thin and thick | – | – | 1 (0·9–1·2) |
| Barnhill 1996[19] | U.S.A. | 537 | Multicentric | 251 | 286 | Thin and thick | 92% | 86% | – |
| Nagore 2005[20] | Spain | 813 | Monocentric | 85 | 728 | Thin and thick | 88·2% | 88·9% | – |
| Testori 2009[21] | Italy | 1055 | Multicentric | 362 | 693 | Thin and thick | 93·5% | 83·1% | – |
| Callender 2011[22] | Sunbelt | 2501 | Sunbelt trial | 261 | 2240 | ≥ 1 mm | – | – | 0·97 (0·73–1·26) |
| Ribero 2013[23] | Italy | 1693 | Monocentric | 349 | 1344 | Thin and thick | – | – | 0·34 (0·19–0·63) |
| Ito 2015[24] | Japan | 110 | Monocentric | 13 | 97 | Thin and thick | – | – | 2·04 (0·69–6·03) |

HR, hazard ratio; CI, confidence interval.

Histological description of regression was reported in nine papers.[15–23] In three studies, the presence of histological regression was significantly associated with a better prognosis,[19,21,23] while in seven it was not significantly associated with survival.[15–18,20,22,24] All studies reported clinical data of the patients on sex and age. Among them, data on Breslow thickness, which is the major prognostic factor in patients with melanoma, were described as the mean depth in two studies[16,23] or as the median in one.[20] In the remaining seven studies,[15,17–19,21,22,24] Breslow thickness was reported as a categorical cut-off. Ulceration distribution was described in eight of the 10 studies.[15,18–24]

## Outcome of the meta-analysis

In the 10 studies included, patients with histological regression of primary melanoma had a lower likelihood of death (RR 0·77, 95% CI 0·61–0·97) than those without histological regression (Fig. 2). Examination of the funnel plot (Fig. 3) did not reveal evidence of publication bias. Similarly, there was no evidence of

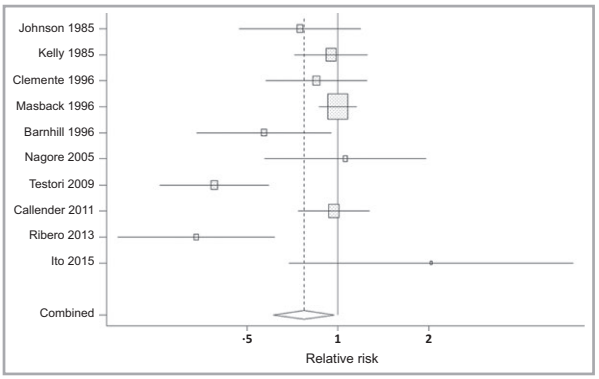


**Fig 2.** Likelihood of death in patients with melanoma with regression. Illustrated are the standardized relative risks of death for the studies included in the meta-analysis. Patients with histological regression of primary melanoma had a lower likelihood of death (rate ratio 0·77, 95% confidence interval 0·61–0·97; darker dashed vertical line) than patients without regression.

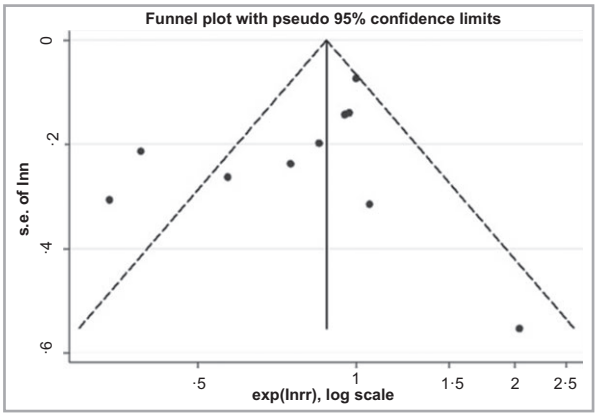


**Fig 3.** Funnel plot of the studies included in the meta-analysis. The funnel plot displays points (each representing an included study) that are evenly and symmetrically distributed, thus showing the absence of study bias and suggesting that the results of the studies are reliable.

such bias for the sensitivity analysis. In fact, it highlights 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 ($P = 0·37$) and Egger test ($P = 0·19$).

When stratified on the main outcome of the studies, the meta-analysis of those studies reporting RR at 5 years was still significant (RR 0·72, 95% CI 0·54–0·98) (Fig. S1), while those reporting HR were not (HR 0·85, 95% CI 0·58–1·26) (Fig. S2). Examination of the funnel plots (Figs S3, S4) 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 patients with melanoma; patients with regression had a lower likelihood to die (RR 0·77, 95% CI 0·61–0·97) than patients without histological regression.

Reported data regarding the prognostic role of histological regression have hitherto been conflicting.[5,25–27] A recent paper on a large cohort of stage I–II patients showed a protective role on prognosis in patients with melanoma with histological regression (American Joint Committee on Cancer stage I–II).[23] At the same time, the discussion regarding SLN performance in thin melanoma with regression has been brought to a conclusion:[28] a meta-analysis has confirmed that histological regression is not a criterion for recommendation of SLN biopsy in thin melanomas.[12]

No solid 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. Tumour regression has been described as an indicator of a tumour-directed immune response.[3] However, tumour-directed T-cell responses may contribute to an improved prognosis as shown by successful treatment with drugs stimulating the immune system's responsiveness.[29–32]

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. Ma *et al.*[33] showed that histological regression results from a T-cell immune response were associated with a decreased risk of nodal progression. In particular, the same authors described a downregulation of the antitumour immunity in the positive SLN with an increase in regulatory T cells, compared with the negative nonsentinel node from the same nodal basin.

Significant heterogeneity with respect to quality characteristics was 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 the literature, and the majority included both thin and thick melanomas, considering consecutive case series of patients. As suggested by scientific literature,[34] meta-analysis in the presence of heterogeneity is commonly performed using a random-effects model, thus we have chosen to use this statistical model to solve this question.

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 the included studies met many of the prior quality metrics, important deficiencies remained.

Another limitation that has to be acknowledged is the use of combined RRs, which we calculated from the data extracted from the selected studies. Furthermore, due to the fact that we

combined different types of measurements, methodological concerns may arise, leading to potential bias.[14,35]

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 evaluation of histological regression was described in the same modality in nine papers out of 10: only Ito *et al.*[24] did not describe how histological regression was evaluated. Indeed, we cannot guarantee the quality of overlapping data. In line with international consensus guidance, further studies are encouraged to utilize more reproducible evaluation features of histological regression, such as the percentage of the lesion regressed (e.g. 50%).[25] This study is also 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 over time from the same institution, and considerable effort was implemented in an attempt to identify and utilize the most suitable reports. However, it is possible 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 standardized reporting of relevant covariates in future observational studies. From a methodological perspective, histological regression needs a worldwide consensus regarding its definition in order to analyse this intriguing feature further. All other prognostic factors should also be collected accurately. It has also been recommended that two pathologists separately assess the histological regression in primary melanoma specimens and that a high interobserver agreement is achieved.

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

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## References

1 Requena C, Botella-Estrada R, Traves V *et al.* Problems in defining melanoma regression and prognostic implication. *Actas Dermosifiliogr* 2009; **100**:759–66.
2 Kang S, Barnhill RL, Mihm MC Jr *et al.* Histologic regression in malignant melanoma: an interobserver concordance study. *J Cutan Pathol* 1993; **20**:126–9.
3 Ribero S, Moscarella E, Ferrara G *et al.* Regression in cutaneous melanoma: a comprehensive review from diagnosis to prognosis. *J Eur Acad Dermatol Venereol* 2016; **30**:2030–7.
4 Blessing K, McLaren KM. Histological regression in primary cutaneous melanoma: recognition, prevalence and significance. *Histopathology* 1992; **20**:315–22.
5 Morton DL, Cochran AJ, Thompson JF *et al.* Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg* 2005; **242**:302–11.
6 Guitart J, Lowe L, Piepkorn M *et al.* Histological characteristics of metastasizing thin melanomas: a case–control study of 43 cases. *Arch Dermatol* 2002; **138**:603–8.
7 Kaur C, Thomas RJ, Desai N *et al.* The correlation of regression in primary melanoma with sentinel lymph node status. *J Clin Pathol* 2008; **61**:297–300.
8 Ribero S, Quaglino P, Osella-Abate S *et al.* Relevance of multiple basins drainage and primary histologic regression in prognosis of trunk melanoma patients with negative sentinel lymph nodes. *J Eur Acad Dermatol Venereol* 2013; **27**:1132–7.
9 Morton DL, Thompson JF, Cochran AJ *et al.* Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med* 2014; **370**:599–609.
10 Ribero S, Osella-Abate S, Sanlorenzo M *et al.* Sentinel lymph node biopsy in thick-melanoma patients (n = 350): what is its prognostic role? *Ann Surg Oncol* 2015; **22**:1967–73.
11 Panic N, Leoncini E, de Belvis G *et al.* Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLOS One* 2013; **8**:e83138.
12 Ribero S, Gualano MR, Osella-Abate S *et al.* Association of histologic regression in primary melanoma with sentinel lymph node status: a systematic review and meta-analysis. *JAMA Dermatol* 2015; **151**:1301–7.
13 Prictor M, Hill S. Cochrane Consumers and Communication Review Group: leading the field on health communication evidence. *J Evid Based Med* 2013; **6**:216–20.
14 Bateson D, Butcher BE, Donovan C *et al.* Risk of venous thromboembolism in women taking the combined oral contraceptive: a systematic review and meta-analysis. *Aust Fam Physician* 2016; **45**:59–64.
15 Johnson OK Jr, Emrich LJ, Karakousis CP *et al.* Comparison of prognostic factors for survival and recurrence in malignant melanoma of the skin, clinical stage I. *Cancer* 1985; **55**:1107–17.
16 Kelly JW, Sagebiel RW, Blois MS. Regression in malignant melanoma. A histologic feature without independent prognostic significance. *Cancer* 1985; **56**:2287–91.
17 Clemente CG, Mihm MC Jr, Bufalino R *et al.* Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. *Cancer* 1996; **77**:1303–10.
18 Måsbäck A, Westerdahl J, Ingvar C *et al.* Cutaneous malignant melanoma in southern Sweden 1965, 1975, and 1985. Prognostic factors and histologic correlations. *Cancer* 1997; **79**:275–83.
19 Barnhill RL, Fine JA, Roush GC, Berwick M. Predicting five-year outcome for patients with cutaneous melanoma in a population-based study. *Cancer* 1996; **78**:427–32.
20 Nagore E, Oliver V, Botella-Estrada R *et al.* Prognostic factors in localized invasive cutaneous melanoma: high value of mitotic rate, vascular invasion and microscopic satellitosis. *Melanoma Res* 2005; **15**:169–77.
21 Testori A, De Salvo GL, Montesco MC *et al.* Clinical considerations on sentinel node biopsy in melanoma from an Italian multicentric study on 1,313 patients (SOLISM-IMI). *Ann Surg Oncol* 2009; **16**:2018–27.
22 Callender GG, Egger ME, Burton AL *et al.* Prognostic implications of anatomic location of primary cutaneous melanoma of 1 mm or thicker. *Am J Surg* 2011; **202**:659–64.

23 Ribero S, Osella-Abate S, Sanlorenzo M *et al.* Prognostic role of regression of primary melanoma in AJCC stage I-II patients. *Br J Dermatol* 2013; **169**:1240–5.
24 Ito T, Wada M, Nagae K *et al.* Acral lentiginous melanoma: who benefits from sentinel lymph node biopsy? *J Am Acad Dermatol* 2015; **72**:71–7.
25 Maurichi A, Miceli R, Camerini T *et al.* Prediction of survival in patients with thin melanoma: results from a multi-institution study. *J Clin Oncol* 2014; **32**:2479–85.
26 Shaw HM, McCarthy SW, McCarthy WH *et al.* Thin regressing malignant melanoma: significance of concurrent regional lymph node metastases. *Histopathology* 1989; **15**:257–65.
27 Ribero S, Osella-Abate S, Pasquali S *et al.* Prognostic role of multiple lymphatic basin drainage in sentinel lymph node-negative trunk melanoma patients: a multicentre study from the Italian Melanoma Intergroup. *Ann Surg Oncol* 2016; **23**:1708–15.
28 Garbe C. Partial histological tumor regression in primary melanoma as protective factor for lymph node micrometastasis. *JAMA Dermatol* 2015; **151**:1291–2.
29 Weber JS, Hamid O, Chasalow SD *et al.* Ipilimumab increases activated T cells and enhances humoral immunity in patients with advanced melanoma. *J Immunother* 2012; **35**:89–97.
30 Robert C, Thomas L, Bondarenko I *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; **364**:2517–26.
31 Robert C, Long GV, Brady B *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; **372**:320–30.
32 Hamid O, Robert C, Daud A *et al.* Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 2013; **369**:134–44.
33 Ma MW, Medicherla RC, Qian M *et al.* Immune response in melanoma: an in-depth analysis of the primary tumor and corresponding sentinel lymph node. *Mod Pathol* 2012; **25**:1000–10.
34 Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009; **172**:137–59.
35 Tierney JF, Stewart LA, Ghersi D *et al.* Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; **8**:16.

## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Fig S1.** Likelihood of death in patients with melanoma with regression (relative risk).

**Fig S2.** Likelihood of death in patients with melanoma with regression (hazard risk).

**Fig S3.** Funnel plot of the studies included in the meta-analysis (relative risk).

**Fig S4.** Funnel plot of the studies included in the meta-analysis (hazard risk).

**Video S1** Author video.