Sentinel lymph node molecular ultrastaging in patients with melanoma: a systematic review and meta-analysis of prognosis

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CRD summary
The authors concluded that polymerase chain reaction-status in sentinel lymph nodes of patients with cutaneous melanoma appears to be of prognostic value, but differences between the studies mean that the results may be overoptimistic and further research is required. The authors' cautious conclusions appears reasonable, but poor reporting of the review methods makes it difficult to assess their reliability.

Authors' objectives
To evaluate the prognostic value of polymerase chain reaction (PCR)-based detection methods for melanoma cells in the sentinel lymph nodes (SLN) of patients with clinical stage I to II cutaneous melanoma.

Searching
MEDLINE, EMBASE, Cancerlit and the Cochrane Library were searched to July 2006; the search terms were not reported. In addition, the reference lists of original reports and reviews were screened.

Study selection
Studies that evaluated the prognostic value of PCR-based detection methods for melanoma cells in the SLN of patients with clinical stage I to II cutaneous melanoma were eligible for inclusion. Studies had to include 50 or more patients and report the TNM stage, disease recurrence rate and/or survival (overall and/or disease-free) for patients stratified by PCR status.

All but one of the included studies used standard haematoxylin and eosin (HE) staining in combination with immunohistochemistry (IHC) for the pathological examination of SLN. The specific antibodies used in IHC staining were reported. An SLN was classified as positive if melanoma cells were identified after HE staining or if a positive IHC result was found for at least one tumour marker. The median duration of follow-up, where reported, ranged from 12 to 67 months.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed by considering the statistical power of each study (details of the methods used were reported).

The authors did not state how the validity assessment was performed.

Data extraction
For each study, the SLN and PCR positivity rates were reported; the review classified an SLN as positive for metastases of melanoma if at least one tumour marker was noted to be amplified at PCR analysis.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Meta-analysis was used to calculate the overall effect of PCR status on survival. The association between PCR and survival was calculated using pooled hazard ratios (HRs); the studies were weighted by the inverse of the variance. For studies presenting univariate survival analysis, HRs were calculated from survival curves. For disease stage and recurrence, pooled odds ratios (ORs) with 95% confidence interval (CIs) were calculated. Statistical heterogeneity was
assessed using the $\chi^2$ and $I^2$ statistics. Random-effects models were used where significant heterogeneity was found.

Sensitivity analysis was conducted by omitting each study in turn and by limiting the analysis to studies reporting multivariate Cox models. Meta-regression was used to examine the influence of year of publication, sample size, type of SLN sampling (bivalving or other), type of PCR (standard or other), number of tumour markers for PCR (single or multiple), length of follow-up, and PCR-positive rates in pathology-negative SLN. Studies that accounted for heterogeneity were identified. Publication bias was assessed using a funnel plot and Egger’s test.

**Results of the review**

Twenty-two studies ($n=4,019$) were included.

**Disease stage and recurrence.**

PCR positivity rates were significantly higher in patients with stage I or II disease compared with stage III disease: 95.1% versus 46.6% ($p<0.001$); the OR was 22.3 (95% CI: 14.7, 33.9; 20 studies, $n=2,249$). All studies used adequate sample sizes. Disease recurrence was significantly higher among PCR-positive patients than PCR-negative patients: 16.8% versus 8.7% ($p<0.0001$); the OR was 2.11, 95% CI: 1.69, 2.63; 15 studies, $n=3,034$). The sensitivity was 57.4% (95% CI: 52.1, 62.5), the specificity 61.1% (95% CI: 59.2, 62.9), the positive predictive value 16.8% (95% CI: 14.8, 19.0) and the negative predictive value 91.3% (95% CI: 89.9, 92.5).

**Survival.**

Overall survival (8 studies, $n=2,140$): 5 studies reported a significant correlation between overall survival and PCR status, while 3 studies reported negative results. The risk of death was significantly increased among PCR-positive patients compared with PCR-negative patients (HR 5.08, 95% CI: 1.83, 14.08, $p=0.002$). Significant heterogeneity was found ($p<0.0001$; $I^2=87.1$%). The results were similar after including only studies reporting the Cox multivariate model. Two studies appeared to account for the heterogeneity (their characteristics were discussed). Meta-regression showed that none of the covariates were significantly associated with HRs. There was no evidence of publication bias from the funnel plot or Egger’s test ($p=0.94$). None of the studies estimated the sample size based on this outcome.

Disease-free survival (13 studies, $n=1,292$): 10 studies reported a significant correlation between disease-free survival and PCR status, while 3 studies reported negative results. The risk of disease progression was significantly increased among PCR-positive patients compared with PCR-negative patients (HR 3.41, 95% CI: 1.86, 6.24, $p<0.0001$). Significant heterogeneity was found ($p<0.0001$; $I^2=94.4$%). The results were similar after including only studies reporting the Cox multivariate model. Four studies appeared to account for the heterogeneity. Meta-regression showed that none of the covariates were significantly associated with HRs. Eight studies were considered to have adequate sample size.

**Authors’ conclusions**

The PCR status of SLN appeared to be of prognostic value in patients with cutaneous melanoma, but differences between the studies indicated that caution is required when considering these findings and further research is required.

**CRD commentary**

The review question was stated clearly. Several relevant sources were searched but the search terms were not reported. No attempts to minimise either publication or language bias were reported. The potential for publication bias was assessed and no evidence of it was found. The validity assessment was limited to a consideration of statistical power, so it is difficult to determine the reliability of the evidence presented. In addition, since the methods used to select the studies, assess validity and extract the data were not described, it is not known whether any efforts were made to reduce reviewer error and bias. Appropriate methods were used for the meta-analyses, heterogeneity was assessed, and potential sources of heterogeneity were explored. The authors’ cautious conclusion appears reasonable in view of the differences between the studies, but the lack of reporting of review methods and study quality makes it difficult to comment on the strength of the evidence underpinning these conclusions.

**Implications of the review for practice and research**
Practice: The authors stated that the evidence about the prognostic power of PCR of SLN in patients with cutaneous melanoma is probably inadequate to support the use of PCR status in clinical decision-making.

Research: The authors stated the need for further studies evaluating the prognostic power of PCR of SLN in patients with cutaneous melanoma.

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