Quantitative RT-PCR detection of colorectal tumor cells in peripheral blood: a systematic review

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CRD summary
This review assessed the detection of circulating tumour cells in peripheral blood of colorectal cancer patients with quantitative reverse transcriptase-polymerase chain reaction assays and concluded that there was insufficient evidence to support the integration of these assays to detect circulating tumour cells. Despite some shortcomings in the review, the authors' conservative conclusions are likely to be appropriate.

Authors' objectives
To assess the detection of circulating tumour cells (CTCs) in peripheral blood of colorectal cancer patients with quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) assays.

Searching
PubMed and EMBASE were search for English-language studies from January 1993 to January 2008; search terms were reported. Reference lists of included studies were cross referenced to identify additional articles.

Study selection
Studies that detected colorectal cancer cells in peripheral blood using a quantitative PCR assay were eligible for inclusion; non-quantitative RT-PCR assays were excluded. Marker genes for PCR in included studies comprised carcinoembryonic antigen, cytokeratin 19 and 20 and guanylyl cyclase C; multimarker assays were also used for cancer cell detection. Control genes used for normalisation included: glyceraldehyde 3-phosphate dehydrogenase; β-actin; porphobilinogen deaminase; and β2-microglobulin. Cell separation techniques varied. The cut-off strategies for the presence or absence of circulating tumour cells in blood samples varied between studies. The number of PCR cycles ranged from 20 to 50. The volume of blood samples ranged from 3mL to 20mL. Primary outcomes were disease-free and overall survival. Included studies comprised adenocarcinomas of the colon and rectum at various tumour stages: Dukes A-D, TNM stage I-III and TNM stage I-IV; preoperatively.

Abstracts were apparently read by more than one reviewer; it was unclear how full papers were selected or disagreements were resolved.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors extracted data for disease-free and overall survival for each study. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
A narrative synthesis was reported, supported by tables. Differences between the studies were discussed in the text.

Results of the review
A total of 12 studies were included in the review (n=965, range 27 to 168). Circulating tumour cells were detected in 0.8% to 100% of patients.

In peripheral blood stage dependent-detection of circulating tumour cells was observed (three out of 10 studies) and increased detection was noted in studies that analysed postoperative peripheral blood samples (three out of four studies). For disease-free survival and overall survival based on univariate analysis there was evidence (p<0.05) for an effect of the detection of circulating tumour cells with QRT-PCR (Quantitative Reverse-Transcriptase Polymerase Chain Reaction) (four studies). Detection of circulating tumour cells in peripheral blood was not identified as an
independent predictor of overall survival in any of the included studies.

**Authors’ conclusions**

There was not enough evidence to integrate QRT-PCR assays to detect circulating tumour cells into the management of colorectal cancer. The quantification of circulating tumour cells in peripheral blood could be useful for predicting stage and outcome in colorectal cancer patients.

**CRD commentary**

The review question was clear, but the inclusion criteria were brief. The limited literature search of two electronic databases was restricted to publications in English and it was unclear whether unpublished studies were sought, so language bias could have been present and some studies may have been missed. The methods used for study selection and data extraction were not clearly reported and it was unclear whether appropriate methods were used to reduce error and bias. There was no formal assessment of the quality of the included studies. Given the apparent diversity of the included studies, the decision to employ a narrative synthesis was appropriate. Despite poor reporting of the review process and uncertainty regarding the quality of the included studies, the authors’ conservative conclusions reflected the evidence presented and are likely to be appropriate.

**Implications of the review for practice and research**

**Practice:** The authors did not state implications for practice.

**Research:** The authors stated that further research that used standardised protocols and large multicentre trials was required. There was a requirement for a standardisation of study methodology before circulating tumour cell quantification could be implemented into the routine clinical setting.

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