Diagnostic value of circulating tumor cell detection in bladder and urothelial cancer: systematic review and meta-analysis

Msaouel P, Koutsilieris M

CRD summary
This review found that circulating tumour cell evaluation can confirm tumour diagnosis but sensitivity was too low for initial screening. However, the results suggested that circulating tumour cell evaluation had insufficient accuracy to rule in or rule out bladder cancer. The possibility of bias, study heterogeneity and lack of quality assessment mean that these results should be interpreted cautiously.

Authors' objectives
To evaluate the use of circulating tumour cell detection assays to diagnose bladder and other urothelial cancers and the association of circulating tumour cell positivity with advanced remote disease.

Searching
PubMed and Scopus databases, Google Scholar and the World Health Organisation (WHO) International Clinical Trials Registry Platform were searched to April 2011. Search terms were reported. Reference lists of primary studies and review articles were screened. The review was restricted to studies published in English in peer-reviewed journals.

Study selection
Studies that evaluated circulating tumour cell in patients with bladder cancer and/or urothelial cancer originating from other locations with clearly identified negative controls (including healthy) were eligible for inclusion. Studies had to enrol at least 20 patients with bladder cancer or 30 patients in total. Outcomes of interest were diagnostic accuracy, correlation with stage of disease, recurrence free survival and overall survival.

Included studies were conducted in Germany, Italy, Japan, USA and other. In most patients cancer originated from the bladder. Cancer stage ranged from 0 to IV. Most studies collected blood samples prior to any treatment but in some studies these were collected before or more than seven days after chemotherapy; other studies reported miscellaneous sample collection or did not report on timing. The mean volume of analysed blood samples was 8.6mL (range 2mL to 16mL). Various methods of circulating tumour cell enrichment from peripheral samples were reported. Most studies used polymerase chain reaction (PCR) to detect circulating tumour cell; other methods included Cell Search, immunocytochemistry-based methods and ELISA. The median age range was 21 to 89 years.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Study quality was not formally assessed.

Data extraction
Two reviewers independently extracted data on the number of cases and controls who were positive and negative using each molecular methods. Where 2x2 tables contained cells with zero, 0.5 was added to each cell. These data were used to calculate sensitivity, specificity and positive and negative likelihood ratios (LR+ and LR-) together with 95% confidence intervals (CIs). Odds ratios (OR) for the association of a positive circulating tumour cell result and progression more advanced disease were calculated. Where multiple blood samples were collected, circulating tumour cell status of the pretreatment sample was used. Where multiple pretreatment blood samples were obtained any circulating tumour cell positive result was classed as positive. Disagreements were resolved through discussion.

Methods of synthesis
Results were displayed graphically using forest plots and in summary receiver operating characteristic (SROC) space. Summary estimates were calculated using random-effects models. Heterogeneity was assessed using the Cochrane Q and I².
Sensitivity analysis was conducted by omitting each study from the meta-analysis and omitting studies where multiple markers were used, including results for the single marker with the best sensitivity or specificity. Subgroup analysis was conducted to investigate the influence of variables assessed in at least three studies. Publication bias was assessed using funnel plots and the Egger test.

Results of the review
Eighteen studies (1,472 participants) were included in the diagnostic meta-analysis and 12 studies (534 participants) were included in the meta-analysis of the association of circulating tumour cell with disease stage.

Sensitivity of the circulating tumour cell detection assay for diagnosis of bladder cancer was 35% (95% CI 32% to 38%). Specificity was 89% (95% CI 87% to 91%). The positive likelihood ratio was 3.8 (95% CI 2.0 to 7.3) and the negative likelihood ratio was 0.72 (95% CI 0.64 to 0.81). There was substantial heterogeneity in all analyses (I²≥80%). Sensitivity analyses had little influence on summary estimates. Subgroup analyses were reported for a large number of variables; some significant associations were found.

Circulating tumour cell positive patients were significantly more likely to have advanced disease compared with circulating tumour cell negative patients (OR 5.05, 95% CI 2.49 to 10.26). There was moderate heterogeneity (I²=52%).

There was no evidence of publication bias (p=0.71).

Authors' conclusions
Circulating tumour cell evaluation can confirm tumour diagnosis and identify patients with advanced bladder cancer. The overall low sensitivity mean that circulating tumour cell detection assays should not be used as initial screening tests.

CRD commentary
The review addressed a clear question. Inclusion criteria were defined. The literature search was adequate for published studies, but the restriction of the review to published studies in English risked language and publication biases. This was assessed in the review but the methods used were not appropriate for diagnostic data. Appropriate steps were taken to minimise bias and errors when selecting studies and extracting data. Study quality was not assessed and so the reliability of the included studies was unclear. Methods used to pool data were not based on the more statistically robust bivariate/hierarchical SROC models. Extensive subgroup analyses were conducted to investigate heterogeneity, but did not appear to have been prespecified.

The relatively low summary LR+ (3.8) reported by the review suggested relatively poor accuracy for ruling in a diagnosis of bladder cancer and did not support the authors' conclusions that circulating tumour cell evaluation can confirm tumour diagnosis. The conclusion that circulating tumour cell could not be used as a screening test was supported by the data. The possibility of language and publication biases, heterogeneity across the studies and unclear quality of the included studies mean that this conclusion should also be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that circulating tumour cell should not be used as first-line screening but can be a quick and non-invasive method for confirming cancer diagnosis and as an initial step in cancer staging.

Research: The authors stated that future studies should determine the optimal tumour makers and molecular methods for circulating tumour cell detection, standardise available techniques, investigate potential advantages of multiple marker assays in PCR-based protocols and assess the correlation of circulating tumour cell positive and patient survival.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.