Meta-analysis of fluorescence in situ hybridization and cytology for diagnosis of bladder cancer

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CRD summary
This review concluded that fluorescence in-situ hybridisation (FISH) had high accuracy for detecting bladder cancer, but lower sensitivity for detecting high-stage bladder cancer than that of urine cytology. These conclusions were not supported by the data presented; these showed relatively poor accuracy for FISH and similar sensitivities for detection of high-stage cancer for FISH and cytology.

Authors' objectives
To assess the accuracy of fluorescence in-situ hybridisation (FISH) compared with urine cytology for detection of bladder cancer.

Searching
MEDLINE, EMBASE, The Cochrane library, Chinese Medical Current Content and CNKI were searched from inception to 2008. Search terms were reported. Key words in both English and Chinese were used for searching. Only studies in English or Chinese were included.

Study selection
Studies that compared FISH with urine cytology for detection of bladder cancer that used cystoscopy or pathological examination as the reference standard were eligible for inclusion. Patients who underwent urine cytology served as the control group. Included studies had to report sufficient data to populate 2x2 contingency tables of test performance (number of true positive, false negative, false positive and true negative test results) for more than 80% of participants.

Studies of patients with concomitant pelvic carcinoma, ureteral carcinoma or other urothelial tumours where separate data could not be extracted for bladder cancer were excluded.

Included studies were published between 2000 and 2008. Where reported, study participants were aged between 28 and 94 years. Criteria for a positive bladder cancer test on FISH varied between studies, but in most cases included five or more cells with gains of two or more chromosomes. One study examined chromosomes 9 and 17 and the rest examined chromosomes 3, 7, 9P21 and 17.

Two reviewers independently assessed studies for inclusion. Any disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
Methodological quality of the included studies was assessed using the 14-item QUADAS tool. Criteria rated as yes were assigned a score of 2, criteria rated as unclear were assigned a score of 1 and criteria rated as no were assigned a score of zero. Studies with a total score of more than 15 were classified as high quality and those with a score of 15 or less were classified as low quality.

Two reviewers assessed study quality. Any discrepancies were resolved by discussion or consultation with an expert.

Data extraction
Data were extracted to populate 2x2 contingency tables of test performance for FISH and urine cytology. Estimates of sensitivity, specificity and diagnostic odds ratio (DOR), with 95% confidence intervals (CIs), were calculated for each study and test (FISH and urine cytology).

Two reviewers extracted data. Any discrepancies were resolved by discussion or consultation with an expert.

Methods of synthesis
Pooled estimates of sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios, with 95%
CIs, were calculated for FISH and urine cytology.

Between-study heterogeneity was assessed using $X^2$ for sensitivity and specificity and Cochran's $Q$ for likelihood ratios. Where significant heterogeneity was present, pooled estimates were calculated using a random-effects model, otherwise a fixed-effect model was used. $I^2$ was used to quantify inconsistency.

Threshold effect (negative association between sensitivity and specificity) was assessed and summary receiver operating characteristic (sROC) curves derived using the Moses and Littenberg model were presented; area under the curve and $Q^*$ value (maximum sensitivity and specificity) were reported.

Results of the review
Twelve studies (3,430 participants) were included in the review. All 12 studies had quality scores between 19 and 26 (median 24) and were classed as high quality.

**FISH**: The pooled estimate for sensitivity was 74% (95% CI 71% to 77%) and for specificity was 88% (95% CI 86% to 90%). The pooled estimate for positive likelihood ratio was 6.18 (95% CI 3.56 to 10.73) and for negative likelihood ratio was 0.29 (95% CI 0.19 to 0.45). The pooled estimate for diagnostic odds ratio was 24.17 (95% CI 9.33 to 62.64). There was significant between-study heterogeneity in all parameters.

**Urine cytology**: The pooled estimate for sensitivity was 57% (95% CI 54% to 61%) and for specificity was 85% (95% CI 83% to 87%). The pooled estimate for positive likelihood ratio was 4.15 (95% CI 2.78 to 6.20) and for negative likelihood ratio was 0.51 (95% CI 0.41 to 0.63). The pooled estimate of diagnostic odds ratio was 9.59 (95% CI 5.91 to 15.57). There was significant between-study heterogeneity in all parameters.

Subgroup data were reported for sensitivity in detecting different pathological grades (G1, G2, and G3) and pathological stages (Ta, T1, and ≥T2).

Authors' conclusions
FISH had a high accuracy for detecting bladder cancer but its sensitivity for detecting high-stage bladder cancer was lower than that of cytology.

CRD commentary
The review stated a clear research objective and defined appropriate inclusion criteria. Several sources were searched for relevant studies. The restriction to English and Chinese raised the possibility of language bias and may have resulted in the omission of relevant studies. Measures to minimise error and/or bias were applied throughout the review process. Methodological quality of the included studies was assessed. Use of an overall quality score is not generally recommended and limits the informative value of the quality assessment.

The validity of generating pooled estimates of accuracy measures is questionable where there is significant between-study heterogeneity. It appeared that the performance of FISH and urine cytology were assessed in different patient groups from non-randomised studies; comparisons between the two tests were, therefore, of very limited value.

The authors' conclusion that FISH had high accuracy was not supported by the data presented, which showed relatively poor test performance. The conclusion that FISH had lower sensitivity than cytology for detection of high-stage cancers was also problematic, as the reported sensitivities appeared similar and no statistical test of difference was reported.

Implications of the review for practice and research
**Practice**: The authors stated that FISH could not replace urine cytology, but could be used as an adjunct in pre-operative detection and postoperative monitoring of bladder cancer.

**Research**: The authors stated that larger multicentre randomised trails were lacking.

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