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Title **Systematic Review of the Clinical Effectiveness and Cost Effectiveness of Photodynamic Diagnosis and Urine Biomarkers (FISH, Immunocyt, NMP22) And Cytology for the Detection and Follow-Up of Bladder Cancer**

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Aim

To assess the clinical and cost effectiveness of photodynamic diagnosis (PDD) compared to white light cystoscopy (WLC), urine biomarkers (fluorescence in situ hybridization [FISH], ImmunoCyt, NMP22), and cytology in detecting and following-up bladder cancer.

Conclusions and results

The advantages of PDD's higher sensitivity in detecting bladder cancer must be weighed against the disadvantages of a higher false-positive rate. Taking into account the assumptions in the model, strategies involving biomarkers and/or PDD provide additional benefits at a cost that society might be willing to pay. Strategies replacing WLC with PDD provide more life-years, but it is unclear whether they are worth the extra cost. In total, 27 studies reported PDD test performance. In pooled estimates (95% confidence interval [CI]) for patient-level analysis, PDD had higher sensitivity than WLC (92% [80% to 100%] versus 71% [49% to 93%]), but lower specificity (57% [36% to 79%] versus 72% [47% to 96%]). Similar results were found for biopsy-level analysis. The median sensitivities (range) of PDD and WLC for detecting lower risk, less aggressive tumors were similar for patient-level detection (92% [20% to 95%] versus 95% [8% to 100%]), but sensitivity was higher for PDD than for WLC in biopsy-level detection (96% [88% to 100%] versus 88% [74% to 100%]). For more aggressive, higher-risk tumors the median sensitivity of PDD for both patient-level (89% [6% to 100%]) and biopsy-level (99% [54% to 100%]) detection was higher than those of WLC (56% [0% to 100%] and 67% [0% to 100%] respectively). Four RCTs comparing PDD with WLC reported effectiveness outcomes. PDD use at transurethral resection of bladder tumor resulted in fewer residual tumors at check cystoscopy (relative risk, RR, 0.37 [95% CI 0.20 to 0.69]) and longer recurrence-free survival (RR 1.37 [95% CI 1.18 to 1.59]) compared with WLC. In 71 studies reporting the performance of biomarkers and cytology in detecting bladder cancer, sensitivity (95% CI) was highest for ImmunoCyt (84% [77% to 91%]) and lowest for cytology (44% [38% to 51%]), whereas specificity was highest for cytology (96% [94% to 98%]) and lowest for ImmunoCyt (75% [68% to 83%]). In the cost-effectiveness analysis, the most effective strategy in terms of true positive cases (44) and life-years (11.66) (flexible cystoscopy [CSC] and ImmunoCyt followed by PDD in initial diagnosis and CSC followed by WLC in follow-up) had an incremental cost per life-year over 270 000 pounds sterling (GBP). The least effective strategy (cytology followed by WLC in initial diagnosis [average cost over 20 years GBP 1403, average life expectancy 11.59]) was most likely to be considered cost-effective when society's willingness to pay was less than GBP 20 000 per life-year. No strategy was cost-effective more than 50% of the time, but 4 of the 8 strategies in the probabilistic sensitivity analysis (3 involving a biomarker or PDD) were each associated with a 20% chance of being considered cost effective. In sensitivity analyses, the results were most sensitive to the pretest probability of disease (5% in the base case).

Recommendations

See Executive Summary http://www.hta.ac.uk/project/1713.asp

Methods

See Executive Summary http://www.hta.ac.uk/project/1713.asp

Further research/reviews required

RCTs including economic evaluations comparing PDD with rigid WLC at TURBT, plus adjuvant immediate single-dose intravesical chemotherapy in patients with diagnosed bladder tumors at CSC.

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