

BLADDER CANCER

Systematic support for photodynamic diagnosis

Two new systematic reviews draw the same encouraging conclusions regarding the utility of fluorescence cystoscopy for the detection of bladder malignancy.

The fluorochrome 5-aminolevulinic acid and its ester derivative hexaminolevulinate can be safely instilled in the bladder, where they preferentially accumulate in neoplastic tissue. Malignant areas appear red, and normal tissue blue, when the bladder surface is illuminated with blue–violet light via a rigid cystoscope.

The most-appropriate role for this ‘photodynamic’ technology in the management of bladder cancer patients has been a topic of heated debate as heterogeneous trial data have accumulated. Now, systematic analyses of published studies have converged on the same conclusion—that photodynamic diagnosis detects more tumors than standard white-light cystoscopy and is associated with prolongation of recurrence-free survival.

Both systematic reviews were compiled by teams in Europe, where hexaminolevulinate (Hexvix[®], licensed to GE Healthcare by Photocure ASA, Oslo) has been approved since 2005 (the product has only just been approved by the US FDA). In the UK, Graham Mowatt and colleagues pooled data from 27 studies. Overall, the sensitivity of photodynamic diagnosis (using either 5-aminolevulinic acid, hexaminolevulinate or hypericin) markedly exceeded that of white-light cystoscopy (92% versus 71%). The difference in sensitivities was more pronounced for more-aggressive, higher-risk tumors.

The superior tumor visualization afforded by photodynamic diagnosis resulted in fewer residual malignancies being detected during follow-up cystoscopy (relative risk 0.37), as well as extension of the average non-recurrence period (relative risk 1.37).

Using Cochrane Collaboration methodology, the authors of the second systematic review sourced data from 17



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high-quality trials. Meta-analysis revealed that fluorescence cystoscopy identified approximately 20% of non-muscle-invasive bladder cancer cases that would have been missed if white-light cystoscopy only had been used. Patients diagnosed photodynamically were 20% less likely to harbor residual tumor. This more-favorable outcome was associated with prolongation of recurrence-free survival.

So, fluorescence cystoscopy is a more-sensitive means of detecting bladder malignancy than standard cystoscopy, but what of specificity? This contentious issue was addressed by both systematic review teams. Both found the specificity of photodynamic diagnosis to be inferior to that of white-light cystoscopy (by up to 15%). Specificity seems to be particularly compromised by recent transurethral resection, instillation of bacillus Calmette–Guérin, or urinary tract infection.

The apparent advantages of photodynamic techniques—superior diagnostic accuracy and outcomes—must, therefore, be weighed against the disadvantage of a higher false-positive rate. A panel of European experts, convened

by GE Healthcare, has concluded that the benefits outweigh the drawbacks. In a paper published in *European Urology*, the panel contends that the number of false-positive diagnoses associated with fluorescence cystoscopy has been progressively dropping, and will continue to do so as the technology is refined and operator experience increases.

Led by J. Alfred Witjes from UMC St Radboud in The Netherlands, the panel has made specific recommendations regarding most-appropriate application of hexaminolevulinate-based fluorescence cystoscopy. They advocate its use in all patients undergoing primary resection for suspected bladder cancer, for recurrence monitoring in patients not previously staged using hexaminolevulinate, for surveillance, and as a training tool.

The clinical benefits of widespread adoption of these recommendations are clear, but what of the cost? Photodynamic cystoscopy requires a specialized endoscope configured for both white-light and fluorescence. Intravesical instillation of fluorochrome, and photodynamic examination during resection, add about 30 min to standard procedure times. Unsurprisingly perhaps, modeling by Mowatt *et al.* showed that the most-effective management strategies were the most expensive. It remains to be seen whether society is willing to bear the extra costs to reap the extra benefits.

Suzanne J. Farley

Original articles Mowatt, G. *et al.* 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. *Health Technol. Assess.* **14**, 1–331 (2010) | Kausch, I. *et al.* Photodynamic diagnosis in non-muscle-invasive bladder cancer: a systematic review and cumulative analysis of prospective studies. *Eur. Urol.* doi:10.1016/j.eururo.2009.11.041 | Witjes, J.A. *et al.* Hexaminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: review of the evidence and recommendations. *Eur. Urol.* doi:10.1016/j.eururo.2010.01.025