Should we screen for bladder cancer in a high-risk population? A cost per life-year saved analysis
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The authors studied a screening programme for bladder cancer in a high-risk population. The screening programme involved bladder tumour markers such as NMP22.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population included a hypothetical cohort of persons aged 50 years who were at high risk for bladder cancer because of heavy smoking or significant occupational exposure.

Setting
The setting of the study was not explicitly stated, but it appears to have been either primary or secondary care or a combination of the two. The economic study was undertaken in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1983 and 2005. The years to which resource use referred were not reported. The reported costs were for 2005 and the price year was 2005.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies.

Modelling
A Markov decision analysis model was used to estimate the cumulative cancer-related survival and costs for a population screened, or not screened, for bladder cancer with NMP22 over a 5-year period. The Markov model was designed using Treeage Pro Healthcare software. The model assumed that a patient would enter at age 50 at high risk for bladder cancer, although the model permitted variations in baseline age of screening by modifying mortality due to other causes. Patients in the standard group either had cancer or no cancer at a rate dependent on cancer incidence. Patients found to have bladder tumours were treated with a transurethral resection and entered one of four bladder cancer disease states:
low-grade superficial (American Joint Committee on Cancer (AJCC) Stage T0, Tis, T1);
high-grade superficial (AJCC Stage T0, Tis, T1); muscle invasive (AJCC Stage T2-T4); or metastatic disease.

The model assumed a simple pattern of disease progression that occurred in a fixed sequence of health states. At the conclusion of each 12-month cycle, the patient could be considered disease-free and undergo routine surveillance, experience recurrence or progression of their disease, or die of unrelated causes. Patients with metastatic disease could die of their disease, die of other causes, or remain in the metastatic state. Patients with high-grade superficial disease received bacillus Calmette-Guerin (BCG) treatment. Patients diagnosed with muscle-invasive disease underwent immediate radical cystectomy with pelvic node dissection. Patients with muscle-invasive disease were assumed to undergo treatment with chemotherapy. Patients diagnosed with metastatic disease received 4 cycles of chemotherapy.

**Outcomes assessed in the review**
The outcomes assessed from the literature were:

- the bladder cancer incidence rates for a high-risk population;
- the bladder cancer stage and grade distributions;
- the rates of downstaging with screening;
- marker sensitivity and specificity for different grade and stage of disease;
- the rates of recurrence and progression for low-grade and high-grade superficial stage of bladder cancer;
- the rate of progression to metastases after cystectomy;
- the rate of death for patients with metastases, after chemotherapy; the cancer-specific death rates in patients with metastatic disease who received chemotherapy; and the yearly risk of dying from other causes.

**Study designs and other criteria for inclusion in the review**
It was not stated whether a systematic review of the literature was undertaken to identify the primary studies. Bladder cancer incidence rates came from a large cohort study. Bladder cancer stage distributions were based on the National Cancer Database which was reported to include 70,000 patients. Cancer-specific death rates in patients with metastatic disease who received chemotherapy were reported to have been obtained from a large multi-centre Phase III study.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Approximately 13 studies were included in the review.
**Methods of combining primary studies**
The authors reported that weighted means were used to determine grade distributions and recurrence and progression rates when more than one study was utilised.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The bladder cancer incidence rate found in the literature was 6%. However, an incidence rate of 4% was assumed in the model because a proportion of the patients in the study from the literature had haematuria and the present analysis was concerned with asymptomatic high-risk patients.

The bladder cancer stage distributions were as follows:

- Stage 0, 44.3%;
- Stage I, 28.8%;
- Stage II, 12.9%;
- Stage III, 7%; and
- Stage IV, 6.9%.

The grade distribution for patients with T0 and T1 disease was 29% with WHO Grade 1, 52.6% with Grade 2, and 18.4% with Grade 3.

A downstaging of 80% was found in the literature. However, a more conservative estimate of 50% was assumed in the model.

Marker sensitivity was 0.61 (range: 0.35 to 0.81) for low-grade disease and 0.79 (range: 0.63 to 0.89) for high-grade disease. The specificity of the marker was 0.86 (range: 0.84 to 0.88).

The rate of recurrence at the superficial stage of bladder cancer for low-grade disease was 30% for year 1, 10% for year 2, 5% for year 3, 5% for year 4, and 5% for year 5. For high-grade disease it was 35% for year 1, 15% for year 2, 5% for year 3, 3% for year 4, and 3% for year 5.

The rate of progression at the superficial stage for low-grade disease was 4% for year 1, 2% for year 3, 1% for year 4, and 1% for year 5. For high-grade disease it was 10% for year 1, 10% for year 2, 5% for year 3, 3% for year 4, and 2% for year 5.

The rate of progression to metastases after cystectomy was 25% for year 1, 13% for year 2, 8% for year 3, 4% for year 4, and 4% for year 5.

The rate of death from bladder cancer in patients with metastatic disease after chemotherapy was 42% in year 1, 80% in year 2, and 50% in year 3.

The yearly rate of death from other causes was 0.65%.

**Measure of benefits used in the economic analysis**
The measure of benefit used was the life-years saved (LYS).
Direct costs
The authors did not explicitly report whose direct costs were included in the analysis. The direct costs included were for the NMP22 test, office cystoscopy, cytology, intravenous pyelogram, computed tomography scan, office visit, transurethral resection of bladder tumour, BCG, cystectomy, chemotherapy, yearly cost of metastatic disease, and the last 6 months of life. The unit costs were not presented separately from the quantities of resources used, most costs being reported as macro-categories. The costs came from Medicare reimbursement and local hospital costs. All costs were updated to 2005 with the gross domestic product deflator inflation calculator. An annual discount rate of 3% was applied to all future costs.

Statistical analysis of costs
The costs were treated as point estimates.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
Both one- and two-way sensitivity analyses were carried out. The parameters varied were the costs of treatment for different stage cancers, cancer incidence, marker variable (cost, sensitivity and specificity) and risk reduction from screening. Two-way sensitivity analyses compared the screening and standard strategies based on best cost-effectiveness. An additional analysis was performed to adjust the interval of screening patients.

Estimated benefits used in the economic analysis
The authors did not report the benefits of each strategy separately (see the 'Synthesis of Costs and Benefits' section).

Cost results
The authors did not report the mean or total costs of each strategy.

Synthesis of costs and benefits
The costs and benefits were combined by calculating the cost (saving) per LYS. In the base-case, screening for bladder cancer in a population with an annual 4% incidence of bladder cancer resulted in a gain of 3.0 life-years per 1,000 patients at a cost-saving of $101,000 for the population, assuming a 50% downstaging in the screened population from muscle-invasive to non muscle-invasive disease.

The cancer incidence had the greatest impact on the cost-effectiveness of screening. At a 2% annual cancer incidence, screening resulted in a gain of 1.48 life-years per 1,000 patients at a saving of $16,000. An annual incidence of 1% resulted in a gain of 0.7 life-years at a cost of $35,358 per LYS.

The one-way sensitivity analyses showed that screening was the most cost-effective strategy (compared with the standard identification of bladder cancer) as long as the cancer incidence was greater than 1.6%, tumour marker costs were less than $126, marker sensitivity was greater than 26%, marker specificity was greater than 54%, downstaging with screening was greater than 20%, and office cystoscopy costs were less than $694.

The two-way sensitivity analyses showed that the incidence of cancer greatly influenced both the risk reduction and the cost required for a screening test to be cost-effective. The greater the possibility of downstaging bladder cancer, the lower the incidence of disease necessary for screening to be cost-effective. At a 1% incidence, a marker would need to
result in a downstaging of 80% to remain cost-effective. However, with an incidence of 4%, screening was cost-effective if downstaging was greater than 20%.

The specificity and sensitivity of the marker had a significant impact on the cost-effectiveness of screening. At a cancer incidence of 4%, a tumour marker specificity of 86% yielded a discounted cost per LYS saved of $101,000. A decrease in specificity to 50% resulted in a discounted cost per LYS of $4,384, while a specificity of 30% increased costs to $25,599 per LYS.

Authors’ conclusions
Urine-based markers are cost-effective in screening a high-risk population for bladder cancers.

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparator was clear. It was chosen because it represented current practice in the authors’ setting. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The clinical data used in the decision model were derived from published sources. The authors did not state that a systematic review of the literature had been performed, thus it was unclear whether the primary studies were identified using a systematic approach or whether they were used selectively. National databases were used for some data but, in general, few details of the primary sources were provided. This presents difficulties in terms of assessing the validity of the primary studies. It was not reported whether the primary studies were comparable in terms of their study populations and interventions. Weighted means were used in circumstances where more than one study was utilised. All variables used in the model were subject to extensive sensitivity analysis.

Validity of estimate of measure of benefit
The summary benefit measure (LYS) was appropriate for the study question. Life-years have the advantage of being comparable with the benefits of other health care interventions. Discounting was applied to all future health benefits, which was appropriate given the long-term horizon. The authors implied that a utility measure (such as quality-adjusted life-years) would be a more valid and comparable health outcome.

Validity of estimate of costs
The authors did not explicitly state the perspective chosen for the analysis of the costs. However, given the categories of costs included in the analysis, the perspective of the health service payer appears to have been used. The unit costs were reported but the quantities used in the study were not, which will limit the generalisability of the authors’ results. The costs were not reported for each alternative strategy. All costs were subject to extensive sensitivity analysis.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The issue of generalisability to other settings was not explicitly addressed, but would have been enhanced by the extensive sensitivity analysis that was performed. The authors do not appear have presented their results selectively. The model used in the analysis assumed that a patient entered at age 50 years, but the authors did not necessarily reflect this in their conclusions. The results could have been more transparently reported as the costs and benefits associated with each strategy were not reported separately.

The authors acknowledged some further limitations to their study. First, the lack of a randomised trial comparing survival with and without a screening strategy for bladder cancer. Second, the exclusion of quality of life considerations. Finally, the assumption that patients with a false-negative screen would present to their physician when their cancers became symptomatic.
Implications of the study
The authors noted that a prospective randomised trial testing the accuracy of bladder cancer detection in a completely asymptomatic cohort and evaluation of outcomes regarding cancer-specific mortality are needed before a bladder cancer screening policy can be determined.

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Other publications of related interest
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