Investigating postmenopausal bleeding for endometrial cancer: cost-effectiveness of initial diagnostic strategies


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 study compared 11 screening strategies used at initial investigation for endometrial cancer in women with postmenopausal bleeding (PMB). All strategies were compared against a no initial evaluation strategy. The strategies compared were:

- endometrial biopsy (EB);
- ultrasonography (USS) using a 4-mm cut-off point for abnormal endometrial thickness;
- USS using a 5-mm cut-off for abnormal endometrial thickness;
- outpatient hysteroscopy (OPH);
- USS (4-mm cut-off) plus OPH;
- USS (5-mm cut-off) plus OPH;
- USS (4-mm cut-off) plus EB;
- USS (5-mm cut-off) plus OPH;
- EB plus OPH;
- a combination of USS (4-mm cut-off), OPH and EB;
- a combination of USS (5-mm cut-off), OPH and EB; and
- no initial evaluation.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
As this was a modelling study, the target population comprised postmenopausal women aged older than 45 years presenting with PMB. In addition, it was assumed that women had no other genital tract malignancy and no co-morbidities, having a normal age-adjusted life expectancy. Specifically, a woman of 65 years of age with PMB and a 5% prevalence of malignant disease was used for the base-case analysis.
Setting
The setting was not explicitly stated at the outset. However, it appears to have been primary and secondary care. The economic analysis was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1982 and 2003. All cost data were derived from official sources published between 2000 and 2002. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies, augmented by expert opinion and authors’ assumptions.

Modelling
The authors constructed a decision analytic model to investigate the cost-effectiveness of each of the screening strategies. The model was designed using DATA Professional 2001 (TreeAge Software, Williamstown, MA). The time horizon of the model was the patients’ lifetime.

Outcomes assessed in the review
The following input parameters were used in the model:

- the failure rates for EB, USS, OPH, USS plus OPH, USS plus EB, the combination of USS, OPH and EB, and EB conducted after successful OPH and after successful USS;
- the complication rates for dilatation of cervix and curettage of the endometrium;
- the true-positive rates of EB, USS (4 and 5 mm), OPH, and dilatation and curettage;
- the true-positive rates for diagnostic tests carried out conditional on a preceding test result (EB if OPH positive, EB if USS positive, OPH if EB negative and if USS positive, USS 4 mm and 5 mm respectively if EB negative and if OPH negative);
- the false-positive rates for EB, USS (4 and 5 mm), OPH, and dilatation and curettage;
- the prevalence of endometrial cancer;
- the surgical stage of hysterectomy according to the classification of endometrial cancer (localised Stage I to advanced Stages II to IV), namely, the probabilities of Stage I and Stage II to IV at first presentation and at re-presentation, respectively;
- the mortality rate for abdominal hysterectomy in endometrial cancer;
- compliance with treatment in women with local or an advanced stage of endometrial cancer; and
- the 5-year survival rate in women with Stage I disease and advanced disease (Stage II to IV).

Study designs and other criteria for inclusion in the review
Systematic reviews and narrative reviews were included in the review. The authors did not report any further inclusion or exclusion criteria.

Sources searched to identify primary studies
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
Overall, the authors used 7 primary studies as sources of effectiveness data.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
The authors do not appear to have investigated differences between the primary studies.

Results of the review
The failure rate was 0.12 (95% confidence interval, CI: 0.09 to 0.15) for EB, 0.0 (95% CI: 0.0 to 0.02) for USS and 0.05 (95% CI: 0.04 to 0.07) for OPH.

The complication rate of dilatation and curettage was 0.014.

The true-positive rate was 0.94 (95% CI: 0.84 to 0.99) for EB, 0.99 (95% CI: 0.97 to 1.0) for USS 4 mm, 0.97 (95% CI: 0.94 to 0.98) for USS 5 mm and 0.86 (95% CI: 0.84 to 0.89) for OPH.

The false-positive rate was 0.01 (95% CI: 0.0 to 0.02) for EB, 0.51 (95% CI: 0.49 to 0.54) for USS 4 mm, 0.45 (95% CI: 0.43 to 0.47) for USS 5 mm and 0.01 (95% CI: 0.0 to 0.06) for OPH.

The prevalence of endometrial cancer was 0.05 (95% CI: 0.03 to 0.10).

The probabilities of Stage I and Stage II to IV at first presentation were 0.7 (range: 0.6 to 0.8) and 0.3 (range: 0.2 to 0.4), respectively.

The mortality rate from endometrial cancer was 0.4% in a woman aged 45 years, 0.8% at 55 years, 1.4% at 65 years and 3.5% at 75 years.

The 5-year survival rate was 87% for Stage I disease and 60% for advanced (Stage II to IV) disease.

Methods used to derive estimates of effectiveness
Some estimates of effectiveness were derived using the opinions of an expert panel. An expert clinical panel was formed to decide upon further investigations conditional upon initial test results. The panel also made decisions in cases of disagreement about the effectiveness estimates.

Estimates of effectiveness and key assumptions
The failure rates of combination strategies, true- and false-positive rates of dilatation and curettage, true-positive rates of screening tests conditional of preceding tests, compliance with treatment, and probabilities of Stage I and Stage II to IV at re-presentation were based on expert opinion. The model was also based on the assumption that all women not
discharged received initial treatment with either total abdominal hysterectomy or bilateral salpingo-oophorectomy, with or without pelvic node sampling.

**Measure of benefits used in the economic analysis**

The measure of benefit was the life-years gained (LYG). For true-positive results, normal actuarial age- or gender-specific death rates were used to estimate life expectancy. For women in Stage I and Stage II to IV endometrial cancer, international 5-year survival data were compared with the expected survival of the general population. It was assumed that the estimated hazard ratio would remain constant for 12 years. After 12 years, survival was assumed to be at the level of the normal population. For false-positive results, age-specific immediate mortality due to unnecessary hysterectomy was applied, after which normal population survival was applied. Future benefits (future years of life) were appropriately discounted.

**Direct costs**

The direct costs used in the analysis were for diagnosis and treatment. The diagnostic costs included pelvic ultrasound scan, OPH, EB, pelvic ultrasound scan plus OPH, OPH plus EB, pelvic ultrasound scan plus OPH and EB, day case hysterectomy or dilatation and curettage, gynaecology outpatient visit FU and failed endometrial biopsy (excluding histopathological examination of endometrial specimen costs). The treatment costs included complex hysterectomy, external beam radiotherapy, chemotherapy, complications, medication (co-amoxiclav 375 mg three times daily), inpatient stay and unplanned laparotomy. The unit costs were reported, but the quantities of resources used were not. The cost data were obtained from official published sources relating to different price years. However, it was explicitly reported that adjustments for inflation were not conducted. The costs were assumed to have been incurred during the first year only, making discounting irrelevant. The price year was not reported.

**Statistical analysis of costs**

The authors reported ranges of unit costs, which corresponded to the interquartile spread derived from published sources.

**Indirect Costs**

The indirect costs were not included in the analysis.

**Currency**

UK pounds sterling ( £ ).

**Sensitivity analysis**

Sensitivity analyses were conducted in order to investigate the robustness of the results to variability in the base-case data. The authors carried out one-way sensitivity analyses for the combination strategies. The parameters investigated were diagnostic feasibility, accuracy, disease prevalence and increase in disease stage due to delayed diagnosis. Multi-way sensitivity analyses were also conducted for all strategies that proved to be cost-effective in the base-case analysis. The parameters investigated were age at presentation, disease prevalence, test failure rates and estimates of diagnostic accuracy. A threshold analysis was also conducted, assuming a cost-effectiveness threshold of 30,000/LYG. The results of the sensitivity analyses were plotted graphically using cost-effectiveness planes.

**Estimated benefits used in the economic analysis**

All strategies demonstrated better survival in comparison with no initial investigation for PMB. The incremental benefits were reported. When compared with no initial investigation:

USS 5 mm resulted in 0.018477 LYG,
USS 4 mm in 0.018839 LYG,
EB in 0.018845 LYG,
OPH in 0.016647,
USS 5 mm plus EB in 0.019706 LYG,
USS 4 mm plus EB in 0.019724 LYG,
USS 5 mm plus OPH in 0.019853 LYG,
USS 4 mm plus OPH in 0.019883 LYG,
EB plus OPH in 0.019731 LYG, and
the combination of USS, EB and OPH in 0.019731 LYG.

It was reported that morbidity due to complications was not taken into account when estimating survival.

**Cost results**
The incremental costs were reported. Each strategy was compared with no initial PMB investigation:

USS 5 mm resulted in an incremental cost of 211.94,
USS 4 mm in 225.57,
EB in 231.89,
OPH in 239.32,
USS 5 mm plus EB in 371.69,
USS 4 mm plus EB in 383.07,
USS 5 mm plus OPH in 386.91,
USS 4 mm plus OPH in 399.07,
EB plus OPH in 399.06, and
the combination of USS, EB and OPH in 453.06.

**Synthesis of costs and benefits**
An incremental cost-effectiveness analysis was conducted and incremental cost-effectiveness ratios (ICERs) were reported. It was reported that OPH, EB plus OPH, and the combination of USS, EB and OPH were dominated by other strategies. USS 5 mm proved to be the most cost-effective strategy in comparison with no initial investigation, resulting in an ICER of 11,470.

When non-dominated strategies were compared with USS (5 mm cut-off), the ICERs ranged from 37,652 for USS 4 mm to 149,219 for EB plus OPH per additional LYG.

Sensitivity analyses demonstrated that the cost-effectiveness results were most sensitivity to the increase in disease stage due to delayed diagnosis. It was reported that the ICERs for strategies based on initial screening with USS 4 mm or EB fell below the threshold of 30,000 per LYG when the probabilities of upstaging endometrial cancer due to delayed
diagnosis were 6% and 8%, respectively.

Authors' conclusions
The analysis demonstrated that, compared with no initial investigation, ultrasonography (USS) with a 5-mm cut-off point was the most cost-effective strategy. When the threshold of 30,000 per life-year gained (LYG) was applied, endometrial biopsy (EB) and USS with a 4-mm cut-off proved to be cost-effective as well. However, "the choice between EB and USS for initial testing is closely related to patient's age, preference, disease prevalence and the availability of high-quality of USS".

CRD COMMENTARY - Selection of comparators
A justification was provided for the comparators used. They reflected currently available services provided in the authors' setting. You should decide if these represent widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
Some estimates of effectiveness were obtained from published systematic reviews. However, the authors appear to have used data from the available studies selectively, and they did not consider the impact of differences between the studies identified when estimating effectiveness. Where effectiveness parameters were not available in the literature, estimates of effectiveness were based on expert opinion. Although an expert panel was formed, the approach it adopted to derive estimates of effectiveness was not reported.

Validity of estimate of measure of benefit
The authors used LYG as the measure of benefit in the economic analysis. The method used to derive the benefits was explicitly reported.

Validity of estimate of costs
The perspective of the NHS paying for the intervention was adopted in the economic analysis. It appears that all the relevant costs have been included. Although the unit costs were reported, quantities of resources used were not. This will not enable the analysis to be easily reworked for other settings. It was reported that litigation costs for false-negative cases were not included. However, their omission is unlikely to have affected the authors' conclusions. The costs were treated deterministically, but extensive sensitivity analyses on costs were conducted to assess the robustness of the estimates used and the ranges used appear to have been appropriate. The authors did not report any adjustments to the costs or a price year, which will hinder any future inflation exercises.

Other issues
The authors compared their results with a published study and reported consistency in the study findings. The issue of generalisability of the results to other settings was directly addressed. The authors do not appear to have presented their results selectively. Several limitations of the study were reported, most of which referred to assumptions made in relation to the effectiveness estimates used in the model (i.e. accuracy of combination tests, or probability and timing of re-presentation of false negatives). In addition, it was reported that there was a lack of accurate cost data and the best available data were used instead (from official national sources). However, the authors tried to investigate the robustness of the estimates used in sensitivity analyses.

Implications of the study
The authors explicitly recommend that women presenting for the first time with PMB should undergo an initial evaluation with USS or EB. In addition, they recommend that clinical guidelines should incorporate the results of their analysis. The authors called for further research in:

the evaluation of new diagnostic methods,
the accurate estimation of resource use during treatment follow-up and palliative care periods,

the exploration of the effect of staging endometrial cancer clinically (e.g. using magnetic resonance imaging) on therapeutic outcomes,

the assessment of costs and benefits of routine pelvic node dissection, and

the development of disease-specific quality of life instruments for women with PMB and endometrial cancer, in order to allow the conduct of a cost-utility analysis.

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