Validity of intraoperative gross examination of myometrial invasion in patients with endometrial cancer: a meta-analysis

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CRD summary
This review concluded that intraoperative gross examination was useful for estimating the depth of myometrial invasion, for staging endometrial cancer, and could be used with confidence, in clinical practice. Given the limitations of the review, analysis, and included studies, the conclusions and implications for practice seem too strong and should be treated with caution.

Authors' objectives
To evaluate the diagnostic accuracy of intraoperative gross examination, compared with histology, for the assessment of the depth of myometrial invasion, in patients with endometrial cancer.

Searching
MEDLINE, EMBASE, Scopus, The Cochrane Library, and the Internet, using Google Scholar, were searched for studies published in full, in English, to October 2011; the search terms were reported and did not include diagnostic filters. The bibliographies of retrieved articles were searched.

Study selection
Studies that evaluated gross examination during surgery for the assessment of the depth of myometrial invasion, and used histology as the reference standard, in patients with endometrial cancer, were eligible for inclusion.

All the included studies contained patients with stage one cancer, and half included patients with any of the four stages. The ratio of low- to high-risk patients ranged from 1:1.24 to 1:4.57. Where reported, the age of participants ranged from 30 to 94 years. Most studies did not administer treatment before surgery; used pelvic washing, followed by total abdominal hysterectomy, with bilateral salpingo-oophorectomy; and recruited patients without metastases. Half the studies recruited patients without cervical involvement. Tumour size was rarely reported. The use and extent of lymphadenectomy varied across studies.

The authors did not state how many reviewers selected studies.

Assessment of study quality
Study quality was assessed using the adapted 11-point QUADAS tool. The authors did not state how many reviewers assessed study quality.

Data extraction
Two independent reviewers extracted data to construct 2x2 tables of test performance; disagreements were resolved by discussion.

Sensitivity, specificity, positive and negative predictive values, and the diagnostic odds ratio were calculated. Myometrial invasion was classified as low (less than 50% of the uterine wall) or high (50% or more). Study authors were contacted to obtain any missing information.

Methods of synthesis
Pooled estimates of sensitivity and overall accuracy were calculated, using fixed-effect models; specificity, predictive values, and the diagnostic odds ratio were pooled, using random-effects models. Heterogeneity was assessed using $\chi^2$ and $I^2$. Summary receiver operating characteristics curves were produced, using the Moses-Littenberg model.

Meta-regression was used to investigate the impact of the stage of disease and publication date. Sensitivity analyses excluded studies that did not include lymphadenectomy. Publication bias was investigated using the Begg-Mazumdar rank correlation, Egger's regression, and Harbord's regression tests.
Results of the review
Sixteen studies met the inclusion criteria, with 2,567 participants (range 25 to 403). Ten of these recruited a representative patient spectrum, 14 used an acceptable reference standard, nine avoided progression bias, 13 avoided partial verification bias, nine avoided differential verification bias, 12 avoided incorporation bias, three blinded interpreters of the index test, four blinded interpreters of the reference standard, and 10 reported on uninterpretable results.

For intraoperative gross examination, the pooled sensitivity was 75% (95% CI 72 to 78; $I^2=17\%$), specificity was 92% (95% CI 90 to 94; $I^2=33.4\%$), overall accuracy was 87% (95% CI 86 to 88; $I^2=29.3\%$), positive predictive value was 80% (95% CI 76 to 84; $I^2=48\%$), negative predictive value was 89% (95% CI 87 to 92; $I^2=67.7\%$), and diagnostic odds ratio was 36.9 (95% CI 28.7 to 47.4; $I^2=0$).

There was no significant impact from the stage of disease, publication date, or use of lymphadenectomy on the pooled estimates. Egger's test indicated significant publication bias for the negative predictive value.

Authors' conclusions
Intraoperative gross examination was useful for estimating the depth of myometrial invasion, for staging endometrial cancer, and could be used with confidence, in clinical practice.

CRD commentary
The review addressed a clear research question, with reproducible inclusion criteria. Several relevant sources were searched, but only studies published in English were included. No diagnostic filters were used in the search, reducing the risk of missing studies. Data extraction was conducted in duplicate, but it was unclear whether similar methods to reduce error and bias were used for study selection and quality assessment. Appropriate criteria were used to assess study quality; the results were reported in full, but the impact of the identified biases on the pooled estimates was not investigated.

Pooled estimates of sensitivity and specificity were calculated separately, from clinically different studies, making their reliability and generalisability uncertain. Summary receiver operating characteristic curves were produced, but the Moses-Littenberg model was used. More robust models could have been used to pool sensitivity and specificity, while maintaining the within-study relationship between these measures. The authors stated in the text that fixed-effect models were used, but the figures indicated that random-effects models were used for some diagnostic measures; there was no justification for the choice of each model, and it did not seem to be based on the presence of clinical or statistical heterogeneity. The analyses of predictive values showed substantial heterogeneity. The prevalence of the target condition (invasion) was not considered nor investigated, and this could have a substantial impact on diagnostic measures.

Given the limitations of the review, analysis, and included studies, the conclusions and implications for practice seem too strong and should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that intraoperative gross examination was a diagnostic tool with acceptable sensitivity and high specificity for gynaecologists or obstetricians to use with confidence in clinical practice.

Research: The authors stated that ways to improve some performance indicators should be investigated to make the diagnostic values more comparable with those of frozen section biopsy.

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Bibliographic details
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.