Efficacy and safety of endoscopic submucosal dissection for colorectal neoplasia: a systematic review

CRD summary
The review found that endoscopic submucosal dissection was very effective and appeared safe for treating colorectal neoplastic lesions. In view of limitations in the review, including potential selection bias, lack of controlled evidence, use of an inappropriate tool for included study quality assessment, and clinical and statistical differences between the included studies, these conclusions may not be reliable.

Authors' objectives
To assess the efficacy and safety of endoscopic submucosal dissection for removal of colorectal lesions.

Searching
MEDLINE was searched for studies published from 1999 to December 2010. Search terms were reported. Reference lists of identified studies and review articles were checked.

Study selection
Studies of endoscopic submucosal dissection for the removal of colorectal lesions were eligible for inclusion. All outcomes were measured per lesion. Studies with fewer than 10 participants were excluded.

The median age of participants in the included studies was 66 years (range 48 to 71); 32% to 71% were men, where reported. In about half of the studies, the clinical indication for endoscopic submucosal dissection lesion size was over 20 millimetres. A few studies were restricted to participants with small rectal carcinoid tumours. All but two studies were set in Asia (Japan, China or Korea). About half of the studies reported use of endoscopic ultrasound staging in all or selected cases. Most studies used multiple cutting devices and most used a glycerol or hyalonurate solution for submucosal injection. The lesions were located in the rectum or colon and included adenoma, carcinoma in situ, submucosal cancer, and carcinoid tumour. Primary outcomes in the review were complete histologically-verified resection and re-surgery for surgical complications. Secondary outcomes were endoscopically-complete resection, bleeding/perforation, rates of re-surgery for surgical failure (excluding surgical complications) or lesion recurrence, and differences between subgroups by lesion type (carcinoid versus non-carcinoid) or ethnicity (Western versus Asian participants).

Two reviewers independently selected the studies.

Assessment of study quality
Quality assessment took into account whether histological verification was available, whether endoscopic submucosal dissection could be replicated based on the information reported, and whether data on surgical failure were provided.

The authors did not state how many reviewers performed the assessment.

Data extraction
For each study, the rate for each outcome was calculated, along with 95% confidence intervals (CI), with the rate of attempted resection as the denominator. An intention-to-treat approach was used. Study authors were contacted for more information on primary review outcomes, if required.

Two reviewers independently extracted the data, with disagreements resolved by a third reviewer.

Methods of synthesis
Studies were combined to calculate pooled outcome rates and 95% confidence intervals, using a random-effects model unless there were fewer than three studies. Heterogeneity was assessed using I². Where heterogeneity was detected, differences between the studies were investigated by regression models using 26 different methodological and clinical factors.
variables as covariates.

Subgroup analyses were conducted to examine differences by lesion type and ethnicity.

Small study effects were investigated using Egger's test and funnel plots.

**Results of the review**

Twenty-two studies were included in the review with 2,774 participants (range 16 to 400) and 2,841 lesions; the study designs included two randomised controlled trials (RCTs), one prospective series and 19 retrospective studies. Eighteen of the studies clearly reported selection criteria. All studies used histological verification. Twenty studies reported withdrawals due to technical failure. Most studies gave adequate detail to permit replication of the intervention. Other criteria assessed (where relevant) were met by all studies. Median follow-up was 22 months (range six to 43).

The histologically-verified per-lesion resection rate was 88% (95% CI 82 to 92; 22 studies); high heterogeneity ($I^2=91\%$) was attributed to differences between carcinoid versus non-carcinoid series ($p=0.04$) and between Asian versus European series ($p=0.03$). There was no significant evidence of publication bias for this outcome.

The per-lesion rate of surgical intervention following a complication of endoscopic submucosal dissection was 1% (95% CI 0 to 1; 22 studies), with moderate heterogeneity ($I^2=49\%$) that reduced to $I^2=14\%$ with exclusion of an outlying study. The Egger's test for publication bias was significant ($p=0.002$) for this outcome.

Per-lesion rates for secondary outcomes (21 to 22 studies for each outcome) included: endoscopically-complete resection 96% (95% CI 91 to 98; $I^2=94\%$); repeat surgery for endoscopic submucosal dissection failure 2% (95% CI 1 to 4; $I^2=80\%$); bleeding 2% (95% CI 1 to 2; $I^2=69\%$); perforation 4% (95% CI 4 to 6; $I^2=45\%$). Heterogeneity was moderate to high for all these analyses. There were no mortalities. One recurrence was reported (rate 0.07%, 95% CI 0 to 0.2).

**Authors' conclusions**

Endoscopic submucosal dissection was very effective and appeared safe for treating colorectal neoplastic lesions.

**CRD commentary**

The objectives of the review were explicitly stated. Inclusion criteria were appropriate, although it was not entirely clear whether the outcomes were prespecified. Only one database was searched, so it was possible that studies may have been missed. Some efforts were made to minimise the risk of reviewer bias and error, as two reviewers independently selected the studies and extracted the data, but it was unclear how many were involved in quality assessment.

The tool used for quality assessment was designed to assess the quality of studies of diagnostic tests rather than studies of interventions and did not provide sufficient detail on important aspects of study quality such as participant selection methods. Although the methods used to calculate mean incidence rates appeared valid, the review findings were of doubtful clinical applicability due to potential selection bias in the included studies and lack of controls. Most of the data was derived from retrospective observational studies, which generally constitute low quality evidence. The control groups of studies (reported to be RCTs by the authors) were not described; the control groups did not appear to contribute to the analysis. The reliability of the review findings was also limited by high statistical heterogeneity (which was only partially explained) and by indications of publication bias. As the authors noted, there were differences between studies in the surgical techniques used and in the definitions of histological categories, which may also limit the applicability of review findings.

In view of limitations in the review, including potential selection bias, lack of controlled evidence, use of an inappropriate tool for quality assessment, and clinical and statistical heterogeneity between the included studies, the authors' conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that more widespread and systematic implementation of endoscopic submucosal dissection for colorectal lesions in Western countries was required.

**Research:** The authors stated that cohorts of patients with T1 stage rectal cancer treated by endoscopic submucosal...
dissection under a rigorous surveillance protocol were needed that compared long-term oncological results with those of transanal endoscopic microsurgery. The authors recommended a new large prospective study of endoscopic submucosal dissection and a need for technical guidelines to standardise techniques for this intervention.

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