Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis
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CRD summary
The authors concluded that the addition of bevacizumab to cancer therapy significantly increased the risk of gastrointestinal perforation. Their conclusion reflected the evidence presented, but insufficient information on the quality of the included trials and the method used to select the trials makes its reliability uncertain.

Authors' objectives
To assess the risks of gastrointestinal perforation in patients treated with bevacizumab for cancer.

Searching
PubMed (from 1966 to July 2008), Web of Science, and abstracts and virtual presentations from the American Society of Clinical Oncology (2000 to July 2008) were searched for relevant articles; search terms were reported. Food and Drug Administration submission documents, manufacturer package inserts, pertinent review articles, and reference lists from the retrieved articles, were also searched for additional publications. It was unclear if there were any language restrictions.

Study selection
Phase II or III randomised controlled trials (RCTs) were eligible for inclusion if they investigated bevacizumab in addition to concurrent chemotherapy and/or treatment with a biological agent, in patients with cancer, and the events or incidence of gastrointestinal perforation were evaluated. Included trials excluded patients with inadequate hepatic, renal, and haematological function; with uncontrolled hypertension or significant cardiovascular or peripheral vascular disease; who were using aspirin (>325mg per day), non-steroidal anti-inflammatory drugs, or anticoagulants, except prophylactic anticoagulants to maintain vascular device access; who had serious non-healing wounds; who had received major surgery within the previous 28 days; who had pre-existing bleeding diathesis or brain metastasis; and who were pregnant or lactating.

The underlying malignant conditions of the included patients were colorectal cancer, breast cancer, pancreatic cancer, renal cell cancer and non-small-cell lung cancer. Concurrent chemotherapy included many drug treatments; the dose regimens were not outlined in the review. The weekly bevacizumab dose in the included trials was either 2.5 or 5mg per kg; all patients were given the same dose within an intervention arm; and two studies had two treatment arms with patients receiving either 2.5 or 5mg per kg within each arm. Most of the included studies used active controls.

The authors did not state how the papers were selected nor how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed using criteria for concealment of random allocation, completeness of follow-up, and objectivity of outcome measurements.

The reviewers did not state how the validity assessment was performed.

Data extraction
The occurrence of gastrointestinal perforation was extracted from the included trials and assessed using the National Cancer Institute's common terminology criteria for adverse events (versions two or three). The gastrointestinal perforations were separated into all grades or grade five, which was fatal. The proportion of patients with gastrointestinal perforation and the exact 95% confidence intervals (CIs) were calculated for each trial and the relative risks (RRs) were calculated. Contact was also made with manufacturers and trial authors when relevant data were unclear or to confirm when there were no incidents of gastrointestinal perforation reported.
Two authors extracted the data independently and any discrepancies were resolved by consensus.

**Methods of synthesis**
The pooled RRs and 95% CIs were calculated using a fixed-effect model. The Cochran Q and $I^2$ statistics were used to evaluate the statistical heterogeneity across the trials. If statistically significant heterogeneity had been observed, ($p<0.1$), a random-effects model would have been used. Subgroup analyses, based on bevacizumab weekly dose (low, 2.5mg per kg, or high, 5mg per kg) and cancer type were also undertaken. The reviewers explored publication bias for the primary outcome (risk of gastrointestinal perforation) using the Begg-Mazumdar test, and a two-tailed probability of less than 0.05 was considered to be statistically significant.

**Results of the review**
Seventeen RCTs ($n=12,294$) were included; three were Phase II and 14 were Phase III trials. Where reported, the median follow-up ranged from 6.7 months to 28 months. Loss to follow-up ranged from 0% to 34%, which was reported in two trials. There was no evidence of publication bias for gastrointestinal perforation by the Begg-Mazumdar test (one-tailed $p=0.34$, two-tailed $p=0.69$). The authors stated that the quality of all the included trials was acceptable, but only five were double-blind and three did not provide follow-up information.

Among patients who received bevacizumab, the incidence of gastrointestinal perforation was 0.9% (95% CI 0.7 to 1.2; 17 RCTs). The incidence of grade five gastrointestinal perforation (death) was 0.3% (95% CI 0.1 to 0.5; 11 RCTs). The mortality of patients with a gastrointestinal perforation was 21.7% (95% CI 11.5 to 37.0; 11 RCTs). There was a statistically significant increase observed in the risk of gastrointestinal perforation associated with bevacizumab treatment compared with control (RR 2.14, 95% CI 1.19 to 3.85; 16 RCTs).

The risk of gastrointestinal perforation associated with high-dose bevacizumab compared with control remained statistically significant (RR 2.67, 95% CI 1.14 to 6.26; 10 RCTs), but was not statistically significant for low-dose bevacizumab compared with control (eight RCTs). Subgroup analysis by cancer type showed that gastrointestinal perforation associated with bevacizumab compared with control was statistically significant for colorectal cancer (RR 3.10, 95% CI 1.26 to 7.63; six RCTs) and metastatic colorectal cancer (RR 3.68, 95% CI 1.28 to 10.63; five RCTs), but not for breast cancer (four RCTs), non-small cell lung cancer (three RCTs), renal cell carcinoma (two RCTs), nor pancreatic cancer (two RCTs).

There was no statistically significant heterogeneity observed in the $I^2$ tests or the Cochran Q tests for any outcome.

**Authors' conclusions**
The addition of bevacizumab to cancer therapy significantly increased the risk of gastrointestinal perforation compared with controls. This risk could vary with bevacizumab dose and cancer type.

**CRD commentary**
This review addressed a well-defined question and the criteria for the inclusion of trials in the review were clearly stipulated. The search was adequate, but it was unclear if any language restrictions were imposed. The authors reported using methods designed to reduce reviewer bias and errors in the extraction of data, but not in the selection of trials nor for the assessment of methodological quality. There was no summary of the methodological quality of the trials and losses to follow-up were up to 34% in some of them. The trials were appropriately combined in a meta-analysis and no statistically significant heterogeneity was found between them for the outcomes examined.

The authors' conclusions reflected the results of the review, but in the absence of a validity assessment, it is difficult to determine their reliability.

**Implications of the review for practice and research**
**Practice:** The authors stated that identifying patients at high risk of gastrointestinal perforation was necessary to reduce this risk. Patient histories should be assessed for evidence of previous diverticulitis or ulcers, radiation exposure, recent sigmoidoscopy, resection of the primary tumour, gastrointestinal obstruction, and multiple previous surgeries.
Knowledge of the tumour mass involving the bowel wall was particularly important for patients with colorectal cancer and/or renal cell carcinoma. Physicians were also reminded to be vigilant in detecting any symptoms of perforation in the course of bevacizumab treatment.

**Research:** The authors stated that further research was required to evaluate the methods of reducing the risk of gastrointestinal perforation, and to investigate the use of bevacizumab in selected patients, who have recovered from a previous complication.

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