Large Scandinavian trial finds no benefit of aspirin after treatment of colorectal cancer liver metastases

A large Scandinavian phase 3 clinical trial shows that initiating aspirin after curative-intent treatment of colorectal cancer liver metastases does not reduce the risk of recurrence. The findings are published in *The Lancet Gastroenterology & Hepatology*.

Colorectal cancer is one of the most common cancers worldwide, and up to half of patients develop liver metastases during the course of their disease. For these patients, surgery, sometimes combined with local ablative treatment, is the main potentially curative option. However, the risk of cancer recurrence remains high. The ASAC trial was therefore designed to determine whether aspirin, given after curative-intent treatment of liver metastases, could reduce the risk of recurrence.

Background: Aspirin and colorectal cancer

Aspirin has attracted considerable attention as a potential treatment to reduce both the risk of developing cancer and the risk of cancer recurrence. The recently reported ALASCCA trial showed a reduced risk of recurrence when aspirin was initiated as adjuvant treatment after surgery in molecularly selected patients with non-metastatic colorectal cancer. These findings have subsequently been incorporated into clinical guidelines for selected patient groups. In contrast, the Scandinavian ASAC trial found no improvement in disease-free survival when aspirin was initiated after curative-intent treatment of colorectal cancer liver metastases. Together, these findings highlight an important distinction between non-metastatic and metastatic colorectal cancer regarding the potential benefit of aspirin as adjuvant treatment to prevent recurrence.

About the ASAC trial

ASAC was a randomised, double-blind, placebo-controlled phase 3 trial conducted at 14 hospitals in Norway, Sweden, and Denmark, and led by Oslo University Hospital. A total of 466 patients were randomly assigned to receive aspirin 160 mg once daily or placebo following curative-intent treatment of their liver metastases by surgical resection and/or ablation. Of these, 428 patients initiated study treatment and were included in the primary analysis.

No reduction in cancer recurrence

The primary endpoint was disease-free survival, defined as the time until cancer recurrence or death. Aspirin did not reduce the risk of recurrence or death compared with placebo (HR 1.08, 95.44% CI 0.85–1.38). Median disease-free survival was 1.13 years in the aspirin group and 1.40 years in the placebo group. There was also no evidence that the effect of aspirin differed between molecular subgroups, based on mutation status in the genes PIK3CA and KRAS.

“Aspirin is a well-established, inexpensive, and widely available drug, and there is considerable interest in whether it can also reduce the risk of cancer recurrence. Our findings demonstrate why such treatments must be tested in rigorous randomised trials before being

adopted for new patient populations," said Professor Sheraz Yaqub of Oslo University Hospital and the University of Oslo, who led the ASAC trial.

Overall survival and safety

Three years after initiation of study treatment, overall survival was 75.7% in the aspirin group compared with 84.9% in the placebo group (HR for death 1.64, 95% CI 1.01–2.65). Although this secondary endpoint reached statistical significance, the finding should be interpreted cautiously because the trial was not designed or powered primarily to assess overall survival. In addition, detailed data on treatments received after recurrence were not collected as part of the trial protocol, limiting interpretation of the survival difference.

Serious adverse events occurred in 17 of 217 patients (7.8%) in the aspirin group and four of 211 (1.9%) in the placebo group. No deaths were considered related to study treatment.

"The results help define where aspirin may, and may not, have a role in colorectal cancer treatment. While recent evidence supports adjuvant aspirin in selected patients with non-metastatic disease, ASAC shows no benefit from initiating aspirin following curative-intent treatment of colorectal cancer liver metastases. With no demonstrated benefit and a higher rate of serious adverse events, there is no rationale for routinely initiating aspirin in these patients solely to prevent cancer recurrence," said Professor Per Sandström of Linköping University Hospital, national principal investigator for the ASAC trial in Sweden.

Findings apply to starting aspirin after treatment of liver metastases

Importantly, ASAC enrolled patients who were not already taking aspirin. The trial therefore tested the effect of starting aspirin following curative-intent treatment of colorectal cancer liver metastases. It therefore cannot determine the effect of aspirin in patients who were already taking the drug before treatment of their liver metastases.

Previous research suggests that the effects of aspirin may differ across stages and biological subgroups of colorectal cancer. Population-based studies have reported an association between long-term aspirin use and a reduced risk of developing colorectal cancer. Randomised trials have also shown a reduced risk of recurrence when aspirin is initiated as adjuvant treatment in selected patients with PI3K pathway alterations in non-metastatic colorectal cancer.

ASAC tested aspirin initiation in a different clinical setting, following curative-intent treatment of metastatic disease to the liver, and found no benefit.

"It is important to distinguish between starting aspirin as an anticancer treatment and continuing aspirin that is already being taken for another medical indication. ASAC found no benefit from initiating aspirin to prevent recurrence following treatment of colorectal cancer liver metastases. The trial did not study patients who were already taking aspirin, and our findings should therefore not be interpreted as a reason for these patients to stop treatment. Patients with another medical indication for aspirin should continue their prescribed treatment and discuss any changes with their doctor," Yaqub said.

The biological and clinical context matters

The findings add to growing evidence that the effect of aspirin in colorectal cancer is unlikely to be uniform across all patients, stages of disease, and treatment settings. Planned molecular analyses of the ASAC trial will investigate whether tumour biology can help explain the findings and whether specific subgroups of patients might respond differently to aspirin.

"The findings underline that the anticancer effects of aspirin may depend on the biological and clinical context. Understanding why aspirin appears beneficial in some settings but not in patients treated for metastatic colorectal cancer will be important for defining which patients may benefit from aspirin as part of cancer treatment," said Professor Kjetil Taskén of Oslo University Hospital and the University of Oslo, co-principal investigator of the ASAC trial.

A large Scandinavian collaboration

ASAC was an investigator-initiated academic collaboration between HPB centres in Norway, Sweden, and Denmark, coordinated by Oslo University Hospital.

"The ASAC trial demonstrates what can be achieved through close Scandinavian collaboration. By bringing together high-volume centres across three countries, we have been able to provide robust evidence on an important clinical question that could not have been answered by observational studies alone," said Peter Nørgaard Larsen, Senior Consultant in HPB Surgery at Copenhagen University Hospital, Rigshospitalet, and national principal investigator for the ASAC trial in Denmark.

The first results from the ASAC trial were presented as a Late-Breaking oral presentation at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago. The article now published in *The Lancet Gastroenterology & Hepatology* reports the final analyses from the trial.

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