Pharmacological suppression of adrenergic and inflammatory signalling using readily available drugs to lower blood pressure and reduce anxiety decreased the risk of post-surgical colorectal cancer (CRC) recurrence. The pilot COMPIT study, published in the *European Journal of Surgical Oncology*, 6 December, found that the simultaneous administration of propranolol and etodolac significantly reduced the risk of colon cancer recurrence at five years.

"This is the first randomized controlled trial identifying long-term clinical benefits of a combined perioperative blockade of inflammation and adrenergic signalling in CRC patients undergoing surgery with curative intent. Other clinical trials have reported beneficial effects on short-term biomarkers, employing either propranolol alone or propranolol and etodolac," write the authors, led by Shagmar Ben-Eliyahu, from Tel-Aviv University, Israel.

Although surgery to remove primary tumours represents the mainstay of all cancer treatments, the risk of metastases after tumour removal is estimated at 35% for colon cancer patients, with higher risk for patients with more advanced stages of disease. Animal studies have demonstrated that catecholamines and prostaglandins are released as a result of physiological and psychological stress responses to surgery, and that these signalling pathways can act directly on tumour cells to enhance their proliferation, motility, and invasive capacity, and can suppress cell-mediated immunity and increase pro-metastatic cytokines. In preclinical tumour models including breast, colon, lung, melanoma, and leukaemia, simultaneous administration of a β-blocker (propranolol) and COX-2 inhibitor (etodolac) has been shown to reduce postoperative metastasis.

An earlier study by Ben-Eliyahu and colleagues, published in 2017 in *Clinical Cancer Research*, involving 38 patients with early-stage breast cancer who received 11 days of perioperative treatment with propranolol and etodolac, found that the treatment combination inhibited multiple cellular and molecular pathways related to metastasis and disease recurrence. These included reduced activity of pro-metastatic/ pro-inflammatory transcription factors (GATA-1, GATA-2), decreased tumour infiltrating monocytes, and abrogated presurgical increases in serum interleukin-6 (IL-6) and C-reactive protein levels.

Following these positive biomarker indications, the team undertook the current study to investigate the impact of perioperative combined COX-2 and β-adrenergic blockade in patients undergoing colon cancer surgery. "This is a short cheap drug treatment with no significant side effects. We deliberately sought the safest and cheapest drugs capable of lowering the body's stress inflammatory response to surgery, in order to save lives," says Ben-Eliyahu.

Between May 2010 and March 2015, 34 patients newly diagnosed with colorectal cancer, without evidence of metastasis, undergoing surgery were randomised to receive oral propranolol and etodolac (n=16) or placebo (n=18). The 20-day treatment regimen was initiated five days before surgery and ended two weeks after surgery.

Results of the intent-to-treat analysis at five years follow-up showed that 12.5% (2/16) patients in the propranolol and etodolac arm versus 50% (9/18) in the placebo arm experienced recurrence (P=0.033), and that 12.5% (2/16) patients died in the propranolol and etodolac arm versus 22% (4/18) in the placebo arm (P=0.151).

For patients who adhered to the protocol, 0% (0/11) patients in the treatment group versus 47% (8/17) in the placebo group exhibited recurrence (P=0.007), and 0% (0/11) in the treatment group versus 17.6% (3/17) in the placebo group died (P=0.151).

Mean disease-free survival (DFS) was 53.3 months (CI 44.45–62.04) in the treatment arm versus 40.65 months (CI 30.1–51.2) in the control arm (P=0.033). Adverse events were equivalent between

the two groups.

“Given the small sample size of this study, this large effect size is inadequate to provide a good estimation for population effect size. However, the statistical significance evident in DFS rates suggest that this positive effect is unlikely to occur by chance,” write the authors.

Safety concerns have been raised regarding use of NSAIDs and/or beta-blockers in the perioperative context. Specially, perioperative use of the β -1 antagonist metoprolol, (but not non-selective β -antagonists, such as propranolol), were associated in some studies with increased risk for post-operative myocardial infarction, stroke, and death. The authors say that, in the current study, the previous breast cancer study, and two ongoing clinical trials in colorectal cancer and pancreatic cancer they have observed no difference in adverse events between the intervention and placebo groups.

The investigators are currently looking for funding to conduct a large-scale clinical trial, with the intention of recruiting hundreds of colon and rectal cancer patients. However, their ambition is being thwarted by pharmaceutical companies having no financial incentives to support studies on off-patent medicines, and science foundations being reluctant to fund clinical research on drugs. “We seek to save lives without financial gain, and we have received financial support from several Israeli and international sources, but these are insufficient for large clinical studies,” says Ben-Eliyahu.