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Preoperative Repurposed Drugs To Reduce Metastases

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Please note: This is a complementary guide on the use of preoperative repurposed drugs to help reduce metastases in patients with cancer. The full guide, 'Cancer Care: The Role of Repurposed Drugs and Metabolic Interventions in Treating Cancer,' and all scientific references, can be found here: imahealth.org/research/cancer-care

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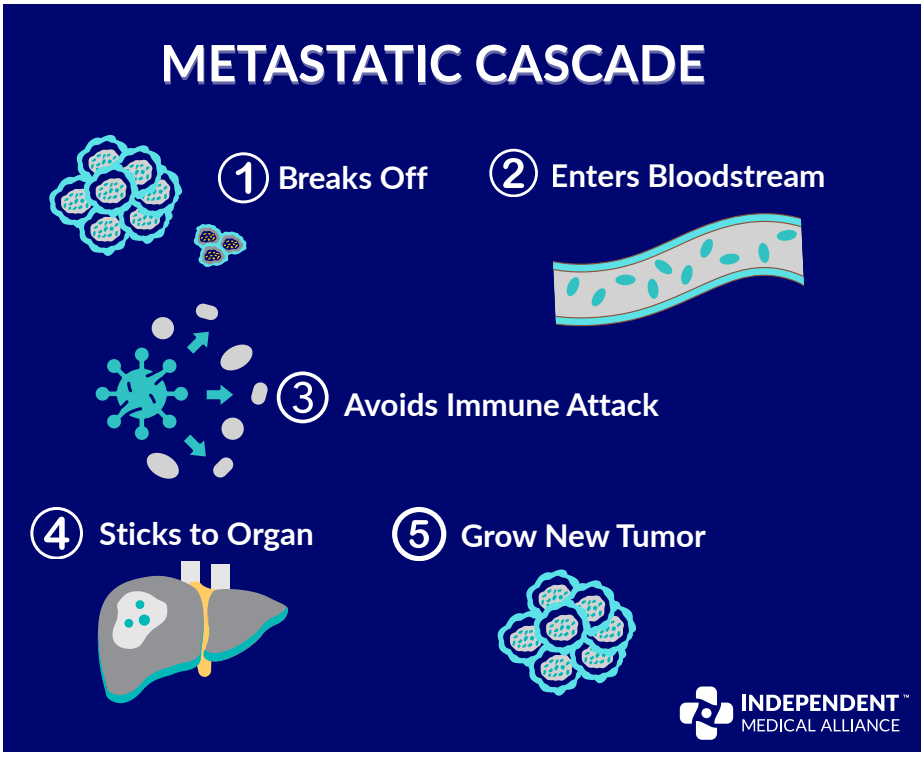
The phenomenon of post-surgical distant recurrence is common across many cancers, including breast, non-small cell lung cancer, osteosarcoma, and others. Among solid tumors, early distant recurrence following surgical resection shows a remarkably consistent pattern—yet little sustained effort has been made to address this problem.

Metastasis—the spread of cancer cells from a primary tumor to distant organs—involves a complex sequence of steps known as the metastatic cascade. (1) While the process is highly inefficient, with most cancer cells failing to complete all stages, a small number of cells may succeed.

Isolated cancer cells that break away from the primary tumor must first breach the connective tissue immediately surrounding the cancer. Once free, the next step is to enter a blood or lymphatic vessel, a process that requires the cancer cell to secrete enzymes that degrade the vessel's basement membrane. Once in circulation, the cell faces turbulence from fast-moving blood, which can damage and destroy it. It must also avoid detection and destruction by white blood cells circulating in the bloodstream. To complete its voyage, the cancer cell must adhere to the lining of the blood vessel, degrade and exit through the basement membrane, and burrow into the surrounding connective tissue to reach its final destination: the target organ. There, it begins to multiply, forming a growing colony that serves as the foundation of a new metastatic tumor. This entire sequence of events must occur quickly, as these cells have a limited life span.



A groundbreaking 2009 study published in the Annals of Surgery reported that cancer surgery can create a physiological environment that significantly reduces the barriers cancer cells normally face. (2) Surgical removal of a tumor almost always disrupts the structural integrity of the tumor and the blood vessels feeding it. This disruption can lead to cancer cells spilling into the bloodstream or seeding directly into the chest or abdominal cavity. (3,4) This alternate route created by surgery can significantly simplify the path to metastasis.

Cancer surgery triggers increased production of inflammatory cytokines such as interleukin-1 and interleukin-6. (5,6) These signaling molecules elevate the activity of cyclooxygenase-2 (COX-2), a highly potent inflammatory enzyme. COX-2 promotes cancer growth and metastasis by stimulating the formation of new blood vessels that feed the tumor. (7,8) It also increases cancer cell adhesion to blood vessel walls, thereby enhancing the cells' ability to spread to distant sites.

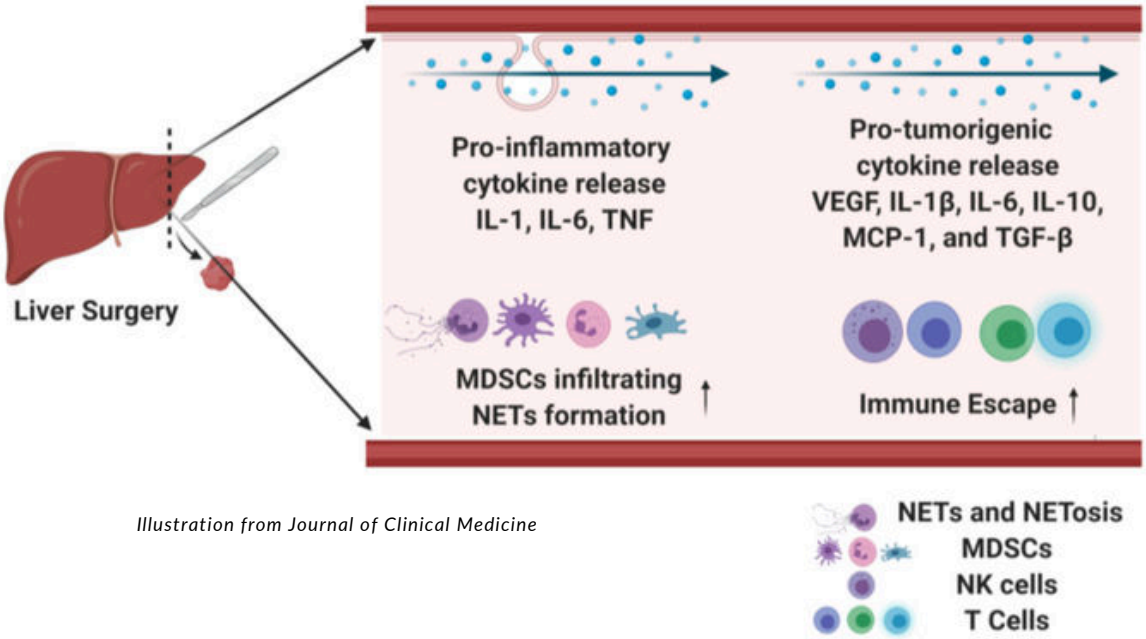
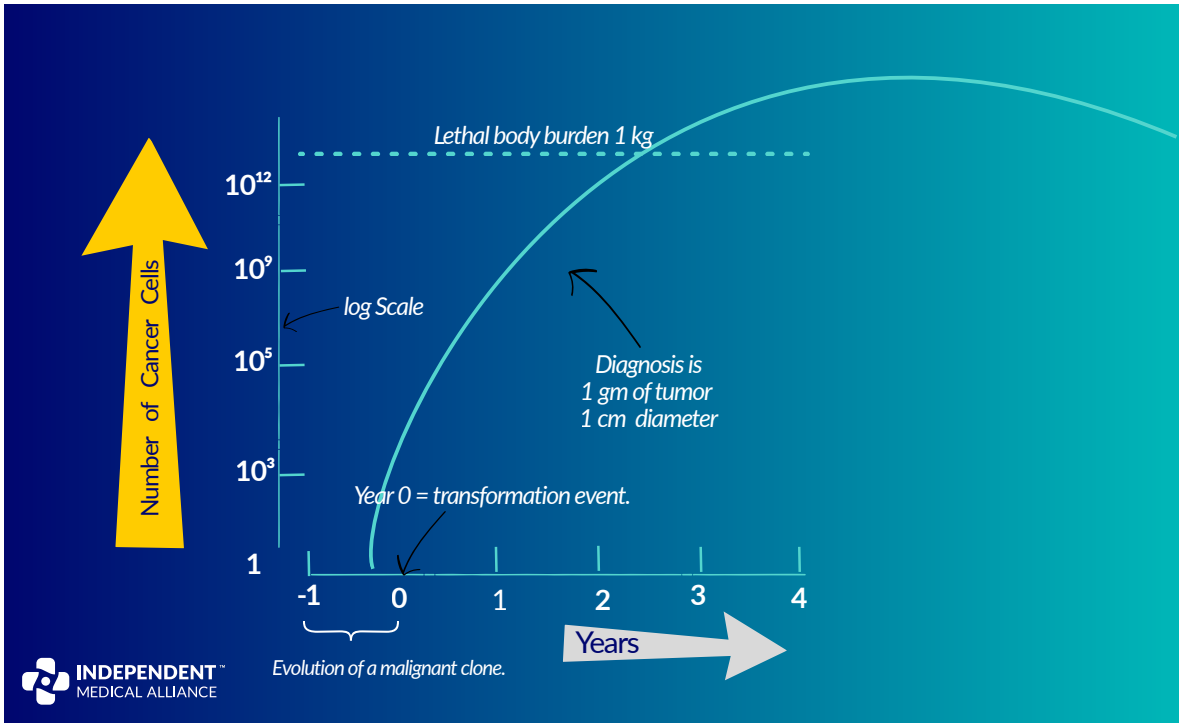


Illustration from Journal of Clinical Medicine

Once a circulating tumor cell reaches its final destination, it must multiply to approximately 1 billion cells before becoming clinically detectable—roughly equivalent to 1 gram of tumor or 1 centimeter in diameter, as shown in Figure 1. Cancer doubling time refers to how long it takes for a tumor to double in volume or for the number of cancer cells to double. This metric is critical for understanding how quickly a cancer grows and can influence prognosis, treatment decisions, and the timing of metastatic spread. Across all cancers, doubling times have been reported to range from as little as 44 days to more than 1,800 days, with averages in some studies between 200 and 325 days. (9-11) This helps explain why metastases from slow-growing tumors may not appear until 10 years or more after definitive surgery. To reach 1 billion cells, about 30 doublings are required.

One study compared the survival among women with breast cancer who underwent surgery and those who did not. (12) As expected, surgery substantially improved early survival. However, further analysis of the data revealed a spike in mortality around year eight in the surgery group—a pattern not observed in the non-surgery group. (12) A worthwhile strategy to guard against this long-term risk is to examine all mechanisms by which surgery promotes metastasis and develop a comprehensive plan to counteract each one.

Figure 1. Tumor burden and growth kinetics



Modified Citrus Pectin

Cancer cells that break away from the primary tumor rely on adhesion to increase their ability to form metastases in distant organs. These cells must cluster together to form colonies capable of expansion and growth; it is unlikely that a single cancer cell can establish a metastatic tumor on its own. Adhesion molecules, such as galectin-3, play a key role in facilitating this clustering. Circulating tumor cells (CTCs) also use galectin-3 on their surface to latch onto the lining of blood vessels—a critical step in the metastatic process. (13)

Modified citrus pectin (MCP) has shown potential in reducing perioperative cancer metastases by targeting mechanisms involved in tumor cell adhesion and dissemination. MCP binds to galectin-3, a protein overexpressed in metastatic cancers that promotes tumor cell aggregation, adhesion to blood vessels, and tissue invasion. (14-16) By inhibiting galectin-3, MCP prevents cancer cells from clustering or attaching to tissues, thereby limiting metastatic spread. (14)

In vitro studies showed that MCP inhibited breast and prostate cancer cell adhesion, migration, and invasion by up to 95% in assays mimicking metastasis.

In a murine model, Nangia-Makke et al. demonstrated that oral administration of MCP significantly inhibited tumor growth, angiogenesis, and spontaneous metastasis of human breast and prostate cancer cells—effects attributed to galectin-3 blockade. (17)

In rats with colon cancer, high-dose MCP reduced the incidence of liver metastases by 40% ($p = 0.008$) and tumor volume by 54% ($p = 0.003$). (16) In prostate cancer models, MCP led to a 50% reduction in lung metastases and an 89% decrease in metastatic colony size. Melanoma studies reported more than 90% fewer lung metastases in MCP-treated mice. In patients with biochemically relapsed prostate cancer, MCP has been associated with limited disease progression. (18) However, clinical trials are still needed to confirm MCP's effectiveness in preventing perioperative metastases in humans.

Propranolol and COX-2 Inhibitors

Perioperative COX-2 inhibition—especially when combined with β-blockers—may attenuate postoperative immune suppression and reduce the risk of metastatic progression. Clinical trials suggest that this combined therapy can improve biomarkers related to tumor metastasis, immune function, and inflammation, and may also enhance long-term disease-free survival in certain types of cancer. (19-21)

Unlike nonselective NSAIDs, which inhibit both COX-1 and COX-2, selective COX-2 inhibitors do not significantly increase the risk of perioperative bleeding or blood loss. (22) While generally considered safe in the perioperative setting, COX-2 inhibitors still raise safety concerns-particularly related to cardiovascular risk and unresolved controversies surrounding their long-term use—which require careful evaluation. (23) Their use should be limited to patients whose cardiovascular profile and overall clinical status support a favorable risk-benefit balance.

Beta-adrenergic signaling is implicated in the post-surgical metastatic process, and numerous in vivo studies have reported that perioperative propranolol is associated with a reduced rate of metastases. (24) In a phase II randomized trial, Hiller et al. evaluated the use of preoperative β-blockade with propranolol on metastatic tumor biomarkers in women undergoing surgery for breast cancer. (25) In this triple-blind, placebo-controlled clinical trial, 60 patients were randomly assigned to receive an escalating dose of oral propranolol (n = 30; 80-160 mg daily) or placebo (n = 30) for seven days prior to surgery.

Propranolol downregulated mesenchymal gene expression in the primary tumor and altered the intratumoral recruitment of neutrophils, natural killer cells, and dendritic cells. It also increased tumor infiltration by CD68+ macrophages (consistent with M1 polarization) and CD8+ T cells. Because the release of pro-inflammatory mediators increases the risk of metastasis, combining propranolol with a COX-2/prostaglandin E2 (PGE2) inhibitor, such as ketorolac or etodolac, may offer a synergistic benefit in the perioperative setting. (26-28)

NCT02596867 is a phase II open-label window of opportunity trial in newly diagnosed breast cancer. (29) Propranolol, at a dose of 1.5 mg/kg twice daily (BID), is administered for three weeks prior to surgical resection. The primary outcome is a reduction in the proliferative index (Ki-67); secondary outcomes relate to safety, toxicity, and adherence.

NCT00888797 is a phase III randomized, placebo-controlled trial of perioperative propranolol and etodolac (a COX-2 inhibitor) in colorectal cancer patients undergoing resection (COMPIT trial). (29) Patients in the treatment arm receive etodolac 800 mg BID throughout the intervention, along with a tapering schedule of propranolol: 20 mg BID for five preoperative days, 80 mg BID on the day of surgery, 40 mg BID during the first postoperative week, and 20 mg orally BID during the second postoperative week.

The primary endpoint is the rate of local and distant recurrence at five years. Preliminary results indicated that adverse event rates were similar between groups. However, intent-to-treat analyses at five-year follow-up showed recurrence in 2 of 16 (12.5%) treated patients compared with 9 of 18 (50%) in the placebo group ($p = 0.033$). (30)

In a landmark study, the incidence of bone metastases in breast cancer patients who received COX-2 inhibitors for at least six months after diagnosis was compared with that of patients who did not take a COX-2 inhibitor. (31) Those taking a COX-2 inhibitor were nearly 80% less likely to develop bone metastases.

Forget and colleagues reported on a retrospective analysis of breast cancer patients treated with conservative surgery, with or without intraoperative NSAIDs (ketorolac or diclofenac). (32) Patients treated pre-incisionally with ketorolac (20-30 mg) or diclofenac (75 mg) showed improved disease-free survival (HR = 0.57; 95% CI, 0.37–0.89; $p = 0.01$) and overall survival (HR = 0.35; 95% CI, 0.17–0.70; $p = 0.03$) compared with those not treated with NSAIDs. (27) However, these findings were not replicated in a prospective randomized trial. (33)

Cimetidine

Cimetidine, an H2 blocker, has shown promising results in improving survival rates for colorectal cancer patients when administered perioperatively. A key study by Adams and Morris demonstrated that a seven-day perioperative course of cimetidine (400 mg BID for five days before surgery and two days after) increased three-year survival from 59% to 93% in 34 patients, though this result was not statistically significant ($p = 0.17$). (34)

Matsumoto performed a similar study in 64 patients undergoing colorectal surgery. (35) One group received cimetidine 800 mg along with 5-fluorouracil 150 mg orally each day for approximately one year, beginning two weeks after surgery. The control group received 5-fluorouracil alone. After a mean follow-up of 31 months, the 3.9-year survival rate was 96.3% in patients treated with cimetidine, compared with 68% in the control group ($p = 0.02$). Subsequent research by the same group provided even more compelling evidence for cimetidine's anti-cancer effects. A longer-term study involving the same cohort demonstrated that the observed benefits were sustained over a 10-year period. (35) The cumulative 10-year survival rate was 84.6% in the cimetidine group versus only 49.8% in controls ($p < 0.0001$). This dramatic difference in long-term outcomes suggests that cimetidine's benefits were more than temporary; they reflected genuine changes in cancer progression and patient prognosis.

Mechanistic studies suggest that cimetidine's anti-cancer effects may result from its ability to inhibit E-selectin expression on vascular endothelial cells. Researchers demonstrated that cimetidine could block the adhesion of colorectal tumor cell lines to endothelial monolayers in vitro and suppress liver metastasis in nude mice. (36) Molecular analyses showed that cimetidine downregulated E-selectin expression without altering E-selectin mRNA levels or affecting nuclear factor κB translocation, suggesting a post-transcriptional mechanism. (36) Importantly, other histamine type 2 receptor antagonists, including famotidine and ranitidine, did not produce similar effects, indicating that cimetidine's anti-cancer actions are independent of conventional histamine receptor blockade. (36,37)

A comprehensive 2012 Cochrane Review analyzed data from six randomized clinical trials involving H2 receptor antagonists as adjuvant treatments for resected colorectal cancer. (28) The review pooled data from 1,229 patients and found a trend toward improved survival when H2 receptor antagonists were used as adjuvant therapy (HR = 0.70; 95% CI, 0.48–1.03; $p = 0.07$). When analyzing only the five cimetidine trials with 421 patients, the meta-analysis found a statistically significant improvement in overall survival (HR = 0.53; 95% CI, 0.32 to 0.87). The authors concluded that cimetidine appears to confer a survival benefit when given as an adjunct to curative surgical resection of colorectal cancers.

The evidence strongly supports the integration of cimetidine into treatment protocols for appropriately selected colorectal cancer patients, particularly those with node-positive disease and tumors expressing high levels of sialyl Lewis antigens. The clinical studies have used various cimetidine dosing regimens, with the most successful trials administering 800 mg orally each day. The original Japanese study initiated treatment two weeks after surgery and continued for one year. The success of cimetidine in colorectal cancer has not been reproduced in other cancers Because cimetidine increases plasma levels of propranolol, the propranolol dose should be carefully adjusted. (38)

Perioperative Protocol Suggestions

The optimal perioperative pharmacologic approach to reducing metastatic disease is unknown, as is the ideal duration of therapy. However, due to a favorable risk-benefit ratio, MCP combined with propranolol should be considered for most patients. MCP at 14 g/day should be initiated at least five days before surgery and continued for six to 12 months postoperatively. Propranolol at a dose of 40 to 80 mg BID is recommended to maintain a resting pulse above 60 to 70 bpm. The propranolol dose should be adjusted carefully in patients also taking cimetidine, and the anesthesiologist should be informed that the patient is taking a beta-blocker. Postoperatively, patients should continue a tapering dose of propranolol for two to four weeks.

Perioperative COX-2 inhibitors should be considered in patients at high risk of metastatic spread who have a favorable cardiac profile. Cimetidine should be considered in patients undergoing surgery for colorectal cancer, at a dose of 800 mg/day beginning at least five days before surgery and continuing for up to one year postoperatively. This regimen should be combined with MCP 14 g/day.

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