Review Article

Perioperative Biobehavioral Interventions to Prevent Cancer Recurrence Through Combined Inhibition of β-Adrenergic and Cyclooxygenase 2 Signaling

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Evidence suggests that excess perioperative activation of the sympathetic nervous system and the consequent release of catecholamines (ie, epinephrine and norepinephrine) in the context of cancer surgery and inflammation may significantly facilitate prometastatic processes. This review first presents biomedical processes that make the perioperative timeframe pivotal in determining long-term cancer outcomes nonproportionally to its short duration (days to weeks). Then, it analyzes the various mechanisms via which the excess release of catecholamines can facilitate the progression of cancer metastases in this context by directly affecting the malignant tissues and by regulating, via indirect pathways, immunological and other mechanisms that affect metastatic progression in the tumor microenvironment and systemically. In addition, this review addresses the need to supplement β-adrenoreceptor blockade with cyclooxygenase 2 inhibition, especially during surgery and shortly thereafter, because similar mechanisms are simultaneously activated by surgery-induced inflammatory responses. Importantly, this review presents translational and clinical evidence showing that perioperative β-adrenoreceptor blockade and cyclooxygenase 2 inhibition can reduce the prometastatic process and cancer recurrence, and the clinical feasibility and safety of this approach are demonstrated as well. Lastly, alternative psychophysiological approaches to the use of β-adrenergic blockers are presented because a substantial portion of patients have medical contraindications to this pharmacological treatment. The adaptation of existing psychophysiological interventions to the perioperative period and principles for constructing new approaches are discussed and exemplified. Overall, pharmacobehavioral interventions, separately or in combination, could transform the perioperative timeframe from being a prominent facilitator of metastatic progression to an opportunity for arresting or eliminating residual disease, potentially improving long-term survival rates in cancer patients. ***Cancer* 2019;125:45-56.** © *2018 American Cancer Society*.

KEYWORDS: adrenergic, β-blocker, cancer, cyclooxygenase 2 (COX2) inhibitor, metastases, perioperative, psychophysiological, psychosocial, stress response, surgery.

PERIOPERATIVE PREVENTION OF METASTASES: AN OVERLOOKED OPPORTUNITY TO IMPROVE CANCER OUTCOMES

In 2012[1] and 2015,[2] at least 8.1 million people and 8.8 million people, respectively, around the world died of cancer. This death toll is equivalent to the entire population of London[3] or New York City[4] and exceeds the population size of 38 of the 50 US states[5] and 15 of the 28 European Union nations.[6] Importantly, metastases account for the great majority of cancer-related deaths (approximately 90% in breast cancer [BC])[7] because our current ability to treat metastatic disease is limited. According to an estimation based on data from various European, American, and Canadian funding agencies, only approximately 5% of research funds around 2006 were devoted to metastasis research.[8] With the current paucity of lifesaving treatments for patients with metastatic disease, the prevention of metastasis is crucial for ensuring patients' survival and holds the greatest potential for improving long-term cancer outcomes.

The perioperative period has been suggested by us and others to provide a window of opportunity for preventing metastases,[9-17] specifically through the inhibition of perioperative stress-inflammatory responses (SIRs) to surgery. Perioperative SIRs promote metastasis directly by affecting tumor cells and indirectly by modulating their microenvironment and interactions with immunocytes.[12] Here we review and discuss 1) prometastatic processes in the perioperative context, 2) perioperative SIRs and their effects on malignant development, 3) the rational and synergistic advantages of using perioperative cyclooxygenase 2 (COX2) inhibition simultaneously with β-adrenergic blockade, 4) preclinical and clinical evidence for the efficacy of perioperative β-blockade and COX2 inhibition (separately and in

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DOI: 10.1002/cncr.31594, **Received:** March 26, 2018; **Revised:** June 22, 2018; **Accepted:** July 13, 2018, **Published online** October 6, 2018 in Wiley Online Library (wileyonlinelibrary.com)

combination), and 5) possible utilization of psychophysiological interventions when β-blockade is medically not feasible or to accompany and improve drug treatment.

THE PERIOPERATIVE CONTEXT: INTENSE PROMOTION OF METASTASIS

An array of perioperative processes have been shown in animal studies to promote postoperative metastatic disease. Among these are 1) psychological distress,[18,19] 2) the use of specific anesthetic and/or analgesic agents and techniques,[20,21] 3) the incision itself and mechanical manipulation of the tumor and its blood vessels,[22-24] 4) hypothermia,[25] 5) blood transfusions,[26] and 6) nociception and pain.[27] Human studies also have provided causal evidence for the significance of the perioperative period. For example, clinical trials using low levels of interleukin 2 (IL-2)[28,29] or progesterone[30] during the short perioperative period have improved overall survival rates for patients with various types of cancer. Accordingly, we and others have suggested the perioperative period as a window of opportunity for arresting postsurgical metastasis.[8,10,12-14,16,31-35]

The aforementioned prometastatic processes are initiated before, during, or after surgery, and some are maintained throughout the entire perioperative period. These processes and the consequent neuroendocrine SIRs that they elicit have been shown to affect tumor cells directly and indirectly through, for example, their impacts on immunity and the malignant microenvironment.[12] The fact that these relatively short-acting processes (in terms of the disease course) are capable of inflicting long-term cancer outcomes, as detailed later, indicates that the short perioperative period is a sensitive and critical timeframe in which metastatic disease may either be promoted or inhibited by a variety of physiological perturbations.[36] Evidence from animal studies lends strong support for this claim and shows that surgery per se enhances tumor cell retention in the lungs, liver, and other target organs,[22,24,37-40] promotes the development of preexisting micrometastases, and increases the postsurgical metastatic load.[24,22] Interestingly, the elimination of the primary tumor may either suppress or enhance progression of minimal residual disease (MRD)[42] by eliminating various progrowth and/or antigrowth and angiogenic factors systemically secreted by the primary tumor. Accordingly, the perioperative period is suggested to be a window of opportunity for influencing the fate of MRD toward fast progression and metastatic outbreak or, alternatively, toward a dormant state or elimination.

Researchers and clinicians are currently studying such perioperative processes and medical routines with the aim of preserving the beneficial effects of surgery while diminishing its deleterious, prometastatic effects.[15,16,31,34,43] Of much recent interest are the use of neuro-axial techniques or regional block,[16,31,44,45] the use of deoxyribonuclease to inhibit the formation of neutrophil extracellular traps,[46] and the perioperative blockade of inflammatory and sympathetic responses,[12,16,43,47] which are detailed later. These endeavors, if successful, may have a profound impact on the course and outcomes of disease.

PERIOPERATIVE SIRs AND THEIR EFFECTS ON METASTASIS

The psychological (eg, fear, anxiety, and fatigue) and physiological effects (eg, incision) of having cancer and undergoing oncological surgery result in perioperative SIRs, which are prominently characterized by excess secretion of catecholamines (CAs; ie, epinephrine [Epi] and norepinephrine [NE]) and prostaglandins (PGs) together with the release of other ligands such as corticosteroids and opioids.[12] These responses are adaptive in coping with naturalistic stressful conditions[48] and also play a role in tissue repair and healing, yet they unfortunately also facilitate many prometastatic processes.[15,17] Although many aspects of stress and inflammation are involved in promalignant processes, here we focus on β-adrenergic signaling and COX2-mediated synthesis of PGs because 1) both have been consistently shown to be key mediators of the impact of stress and surgery on cancer progression and 2) both can be safely addressed clinically with well-established therapeutic agents (ie, propranolol and etodolac; discussed later).

CAs and PGs: Their Role in Perioperative SIRs and Cancer Biology

CAs are secreted in response to sympathetic nervous system (SNS) activation both locally from SNS nerve fibers (releasing NE) and systemically from the adrenal medulla (mostly Epi).[49] Sympathetic signaling regulates the activity of various cell types,[50] including epithelial and most lymphoid and myeloid immune cells, at different sites of cancer initiation and/or progression.[34,51-55] Many tumors are innervated by the SNS, express adrenoceptors, and exhibit higher levels of CAs than their surroundings.[54] Importantly, β-adrenergic signaling has been shown to increase inflammation, angiogenesis, and tumor invasion capacity,[56] predominantly through the

cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) pathway.[49]

CAs bind to α1-, α2-, α3-, β1-, β2-, and β3-receptors. Preclinical and clinical studies have mostly implicated β1- and β2-adrenergic receptors in cancer's progression, although β3- and α-adrenoceptors may also play a role in tumor progression (for a review, see Cole et al[54]). Congruently, preclinical evidence implicates β2-adrenoceptors as the major adrenergic signaling pathways in a variety of tumors and immunocytes[49,52,53,57-60]; thus, β2-blockade may be essential in counteracting adrenergic signaling.[14,54] It was suggested that β-blockers could potentially be selected on the basis of tumor expression of different β-adrenoceptors,[49] and accordingly, we suggest that an assessment of the receptor profile in malignant tissue (extracted at biopsy) could improve optimal perioperative treatment.

Perioperative Costimulatory and Synergistic Effects of CAs and PGs on Prometastatic Processes

The inflammatory and adrenergic responses, though distinct in their pathways, can act synergistically and potentiate each other.[14,40,64] For example, SNS activation can promote the metabolism of arachidonic acid[49] (the building blocks of PGs) and facilitate the synthesis of PGE2,[40] and inflammation can sensitize receptors that convey nociception and consequently induce a sympathetic response[65] (see Fig. 1). Importantly, in some cases, the prometastatic effects of adrenergic signaling have been shown to be dependent on PGE2 synthesis.[40] Recently, Muthuswamy et al[64] reported that COX2 inhibition abolished in vitro immunosuppressive effects induced by either Epi or NE on CD8+ T cells. Furthermore, they showed that chronic stress upregulated COX2 expression in mice and that exposure to Epi/NE induced similar in vitro changes in human breast and colon tissues, effects that were inhibited by the COX2 inhibitor celecoxib. It is noteworthy that the activation of both adrenergic and prostanoid receptors also converges to the same intracellular mechanisms (eg, activation of the cAMP-PKA pathway),[49] and thus they can exert their influence either separately or through their combined effect, which may exceed their individual potency in promoting metastasis, as indeed was shown by Muthusamy et al. In addition, animal studies conducted by us have provided evidence that antagonizing each drug alone may have beneficial effects, yet the combined blockade of adrenergic signaling and PG synthesis has repeatedly been shown to have antimetastatic effects superior to the effects of either drug alone.[9,12] Often, the combined blockade has been the only effective approach.[22,66,67]

SIRs are also known to be induced as an anticipatory response to threatening events,[17,54,68] including public speaking[69,70] and skydiving.[71] Their impacts include elevated levels of Epi, NE, cortisol, and inflammatory cytokines (eg, C-reactive protein and IL-6) alongside immune perturbations. Importantly, similar effects are evident a day before surgery[72] in, for example, BC patients.[68]

Taken together, the preoperative onset of SIRs and their synergistic nature suggest that a combined blockade of these responses should be initiated before surgery to effectively counteract their deleterious effects on cancer progression. It has been hypothesized by us and others that such a blockade will be more efficacious in the initial stages of metastatic development.[12,16,73] Such a state exists in many cancer patients during the perioperative period because MRD in most operated patients is in the form of scattered single tumor cells or micrometastases.

Perioperative SIRs and Their Effects on Metastasis

Both CAs and PGs can directly affect the malignant tissue. The activation of prostanoid or adrenergic membrane receptors in malignant tissue increases levels of cAMP and through it modulates the activation of many transcription pathways. Among these are pathways known to promote metastatic processes, including nuclear factor κB (NF-κB), signal transducer and activator of transcription 3 (STAT3), cyclic adenosine monophosphate response element–binding protein (CREB), activating protein 1 (AP-1), GATA1, activating transcription factor (ATF), and ETS.[49,74] These pathways promote inflammation, angiogenesis, tumor invasion capacity, and epithelial-to-mesenchymal transition (EMT) by increasing tumors' secretion of various prometastatic proteins such as IL-6, IL-8, vascular endothelial growth factor, and matrix metallopeptidase 9 (MMP9) as well as the expression of various receptors (eg, epidermal growth factor receptor).[49,54,74] These processes affect many types of human cancers. For example, the secretion of proinflammatory IL-6 and IL-8 was recently shown in animal models to directly promote the metastasis of sarcomas and carcinomas by enhancing tumor cell migration and motility.[75] Their secretion by tumors was recently suggested to maintain micrometastatic growth before primary tumor excision (R. Haldar and L. Shaashua, Oral communication, October 2017). In addition, a prominent direct effect of both PGs and CAs on tumor cells is the induction of EMT, which is considered a key step

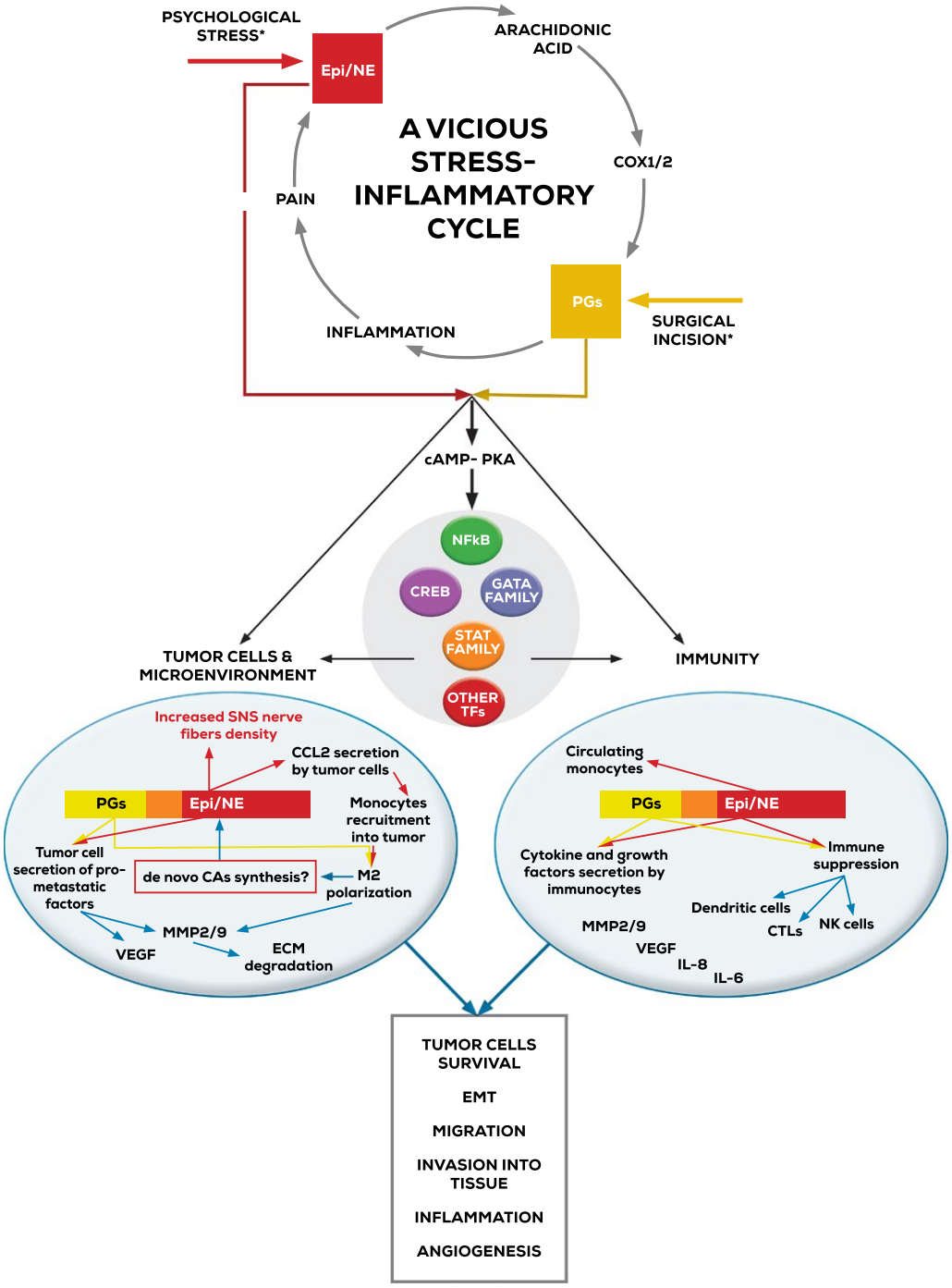

Figure 1. Vicious stress-inflammatory cycle. Psychological stress (eg, fear and anxiety) leads to the release of Epi and NE by SNS nerve fibers and adrenal medulla. The release of Epi and NE promotes the metabolism of arachidonic acid, which leads to PG synthesis, which in turn induces inflammation and pain and leads to further SNS activation. The cAMP-PKA pathway is activated by both PGs and CAs; this leads to diverse prometastatic transcription factor activity (eg, through CREB and NFkB) in tumor cells and their microenvironment and, in various immune cells, promotes prometastatic tumor cell characteristics while reducing the host environment capacity for arresting metastasis. Together, these processes lead to successful tumor cell survival, EMT, migration, invasion into adjacent or distant tissue, inflammation, and angiogenesis, and this results in accelerated growth of metastases (for details, see the Perioperative Costimulatory and Synergistic Effects of CAs and PGs on Prometastatic Processes, Direct Effects of SIRs on Metastasis, and Indirect Effects of SIRs on Metastasis sections). CA indicates catecholamine; cAMP, cyclic adenosine monophosphate; CCL2, C-C motif chemokine ligand 2; COX, cyclooxygenase; CREB, cyclic adenosine monophosphate response element–binding protein; CTL, cytotoxic T cell; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; Epi, epinephrine; IL, interleukin; MMP, matrix metallopeptidase; NE, norepinephrine; NFkB, nuclear factor κB; NK, natural killer; PG, prostaglandin; PKA, protein kinase A; SNS, sympathetic nervous system; STAT, signal transducer and activator of transcription; TF, transcription factor; VEGF, vascular endothelial growth factor. * Both stressors can occur simultaneously.

in the metastatic process.[16,54,62] Importantly, COX2 inhibition was recently shown in vitro to reverse EMT in colorectal and non–small lung cancer cell lines,[76] and β-adrenergic signaling was shown to promote EMT.[77] Taken together, the data show that PGs and CAs directly induce prometastatic changes in tumor cells.

Perioperative SIRs and Their Effects on Metastasis

Prostanoid and β-adrenergic signaling modulates a number of immune processes in a manner that facilitates metastatic progression.[12,16,17,43] Adrenergic signaling increases the numbers of monocytes in the circulation[54] and stimulates tumor cells to secrete chemokines (eg, colony stimulating factor 1 [CSF1] and C-C motif chemokine ligand 2 [CCL2]), which attract monocytes to infiltrate the tumor and evolve into macrophages.[58,78] Within this tumor microenvironment, β2-adrenergic signaling polarizes macrophages to acquire M2-like characteristics and to suppress M1-like characteristics[79] and thereby transforms them into cancer-promoting tumor-associated macrophages, and PGs have been shown to enhance this polarization through the CREB-KLF4 pathway.[80] Importantly, macrophages that exhibit M2-like characteristics have been shown to suppress cell-mediated immunity and promote tumor extravasation and metastasis[79]; they have a pertinent role in tumor progression, especially in its early stages.[54] Indeed, chronic stress has been reported to induce an accumulation of tumor-associated macrophages in tumors and to upregulate their prometastatic gene expression (eg, transforming growth factor β [TGF-β] and COX2).[81] Notably, macrophages are capable of producing de novo CAs in vitro after lipopolysaccharide-induced stimulation and in vivo in response to cold exposure,[82] and this provides a possible non–SNS-dependent source of adrenergic signaling within the tumor microenvironment.[79,83] In addition, β-adrenergic activation increases expression of COX2 and PGs in primary bone marrow–derived macrophages and human monocyte–derived macrophages.[84]

Adrenergic signaling also reduces lymphocyte numbers in the lungs' marginating pool (within the pulmonary capillaries),[67] where circulating tumor cells can be trapped and destroyed, and reduces lymphocyte infiltration into tumor tissues.[54] Many immunocytes, including macrophages, natural killer (NK) cells, and cytotoxic T cells, express receptors for PGs and CAs.[15,48,50,59,63,85] Activation of these receptors often suppresses their cytotoxicity (NK cells[18,86] and cytotoxic T cells[57,63]) and may induce a Th2 dominant profile in the Th1/Th2 cytokine balance, suggested to be pro-metastatic.[16] Thus, adrenergic and PG signaling affects both the numbers and killing capacity of immunocytes in critical compartments of the circulation and within the tumor microenvironment.

In addition to directly affecting immunocytes, PG and β-adrenergic signaling promotes other prometastatic changes in the tumor microenvironment. PGs cause immune and tumor cells to secrete MMP2 and MMP9; this leads to extracellular matrix degradation, which facilitates tumor cell extravasation.[78] Platelet activity is known to be influenced by COX1 activation, and emerging evidence suggests that platelets are involved in various prometastatic processes, including the suppression of NK cell cytotoxicity, the secretion of growth factors, the shielding of tumor cells, and the facilitation of tumor migration and invasion.[87] Furthermore, chronic stress and specifically sympathetic activation were shown to increase lymphatic vascular density and lymphatic flow in various animal models (and also lymphatic flow in humans).[84] These changes were shown to be related to an increased cancer cell presence in lymphatic circulation and lymphatic nodes and were correlated with increased lung metastases. Importantly, these changes were blocked either by a nonselective β-blocker or by a COX2 inhibitor.[84] Another prominent effect of adrenergic activation is the increase in the density of SNS nerve fibers within the tumor microenvironment.[88] Thus, separate and combined effects of PGs and CAs, driving tumor cell dissemination, migration, and survival, are involved in microenvironment changes.

Overall, PG and β-adrenergic signaling promotes a systemic prometastatic environment, facilitates macrophage recruitment into the tumor microenvironment and promotes their M2 phenotype, facilitates tumor EMT, induces prometastatic changes in the lymphatic system, and acts on the tumor and its microenvironment to suppress cell-mediated immunity and to promote inflammation, angiogenesis, migration, and tumor cell survival. During the perioperative period, in which both CAs and PGs are elevated, these multifaceted effects may synergistically culminate in exerting deleterious, prometastatic effects.

INHIBITION OF PERIOPERATIVE SIRs AND ITS EFFECTS ON METASTASIS

The biological rationale for perioperative inhibition of SIRs is robustly supported by translational studies.[12] These studies have shown decreased metastatic loads and increased survival rates in response to perioperative SIR

inhibition in many tumor models. Importantly, although β-blockade and semiselective COX2 inhibition showed beneficial effects separately, their combined use was superior and, in some models, was the only effective approach; this was evident when the β-blocker propranolol was combined with the semiselective COX2 synthesis–inhibitor etodolac.[12,22,33,66,67,84,89] Retrospective clinical studies have provided inconclusive results regarding incidental perioperative or chronic use of β-blockers, with several studies,[90-92] but not others,[93,94] reporting beneficial effects on long-term cancer outcomes, especially with respect to nonselective β-blockade. Perioperative COX inhibition also has provided inconclusive results, as recently reviewed by Cata et al.[43] Notably, aspirin, a nonselective COX inhibitor, was recently recommended for the prevention of colorectal cancer (CRC) in men at risk between the ages of 50 and 59 years.[95,96]

Our ability to draw definitive conclusions based on the aforementioned retrospective studies is limited by 1) the heterogeneity of the drugs used, 2) the types of cancer and cancer stages, 3) different definitions of the perioperative period, 4) the fact that retrospective studies rely on data for patients with various comorbidities,[14,16,17,97] and 5) an immortal time bias (a bias from the inclusion of treated patients who survived postoperatively before taking medication; see Weberpals et al[97] and Suissa[98]).

Although inconclusive, evidence seems to suggest an advantage for nonselective β-blockers (eg, propranolol)[94,99,100] and for both COX1 and COX2 blockade (eg, through the semiselective COX2 inhibitor etodolac).[11,101] It is our hypothesis that because of the abundance of both CAs and PGs during the perioperative period, the combined blockade would be expected to have more reliable and robust benefits.

PERIOPERATIVE RANDOMIZED CONTROLLED TRIALS OF β-BLOCKADE OR COX2 INHIBITION: EFFECTS ON ONCOLOGIC OUTCOMES

Several perioperative randomized controlled trials (RCTs) are ongoing, and a few have already provided initial promising results regarding the effects of the inhibition of either CAs or COX signaling on cancer outcomes and on indices of inflammation and immunity.[16,43] Specifically, 2 RCTs using celecoxib (a selective COX2 inhibitor; n = 32)[102] and low-dose aspirin (n = 40),[95] respectively, showed a slight reduction of systemic inflammatory markers (PG metabolites in urine) during cancer surgery and reduced PGE2 levels in the rectal mucosa of patients undergoing CRC screening.

Studying β-blockers, a recent pilot RCT (n = 22)[91] treated patients with ovarian cancer with propranolol for a total of 5 perioperative days, with the treatment starting 2 days before surgery. The primary outcome was cancer antigen 125 (a biomarker indicating the tumor load), which exhibited a greater postoperative decline in treated patients versus the placebo group and whose levels remained lower for 1 to 3 weeks postoperatively but not thereafter.[32] In a recent RCT conducted by Ramondetta et al[103] in patients with ovarian cancer (n = 32) undergoing either reductive surgery or neoadjuvant chemotherapy, a low dose of propranolol (10-20 mg twice daily), initiated 2 days before treatment, led to an overall improvement in quality of life, anxiety, and depression. Another RCT in patients with ovarian cancer, conducted by Thaker et al,[104] initiated propranolol administration 3 days before surgery (n = 84; 40 mg twice daily) and continued treatment until the end of chemotherapy. Reductions in the serum levels of vascular endothelial growth factor, IL-6, monocyte chemoattractant protein 1 (MCP-1), and IL-8 were noted. In all of the aforementioned RCTs, treatments were well tolerated with no reported drug-related adverse events.

PERIOPERATIVE CLINICAL STUDIES OF COMBINED β-BLOCKADE AND COX2 INHIBITION: EFFECTS ON ONCOLOGIC OUTCOMES

Simultaneous inhibition of sympathetic and inflammatory responses has rarely been studied clinically. Yet, emerging retrospective evidence and a few recent RCTs provide clear positive results in terms of both safety and short-term antimetastatic efficacy. In a recent retrospective study in patients with ovarian cancer, Dood et al[105] found that nonsteroidal anti-inflammatory drug (NSAID) or β-blocker use was correlated with lower mortality, and their synergistic use was correlated with greater positive outcomes.

We have recently conducted 2 RCTs assessing the effects of combined inhibition of COX2 and β-adrenergic signaling in patients with BC[68] (n = 38) and CRC (n = 34).[106] A combined regimen of propranolol and etodolac (or placebo) was initiated 5 days before surgery and continued for 5 days (BC) or 2 weeks (CRC) postoperatively. Propranolol was initiated at 20 mg twice daily, increased to 80 mg twice daily on the day of surgery, and decreased to 20 mg for the remaining period, whereas 400 mg of etodolac was given twice daily throughout the

treatment period. No drug-related adverse events were noted. In both studies, messenger RNA profiling of excised tumors showed decreased EMT; downregulation of the transcriptional activity of CREB, NF-κB, the GATA family, and STAT3; reduced presence of monocytes; and increased presence of NK cells in CRC tissue. In blood samples from BC patients, treatment reduced serum IL-6 and C-reactive protein levels, improved markers of NK cytotoxicity, and enhanced interferon-γ– and IL-12–induced production without affecting anti-inflammatory soluble factors (cortisol and IL-10). In the CRC study, 3-year follow-up showed large but statistically insignificant improvement in disease-free survival, and this suggested the long-term safety of the treatment. These findings clearly show the efficacy of this combined drug paradigm and suggest its metastasis-reducing impact, which should be tested in larger clinical trials.

It should be noted that safety concerns, including cardiovascular and cerebrovascular events and anastomotic leaks, have been raised about the perioperative use of NSAIDs and β-blockers. Yet, when appropriate exclusion criteria are used, the administration of propranolol in titration is initiated at least a few days before surgery, NSAIDs that target mainly COX2 are used, and a relatively short duration of treatment is maintained, many of the safety concerns (eg, cerebrovascular events or gastrointestinal bleeding) may be mitigated. Animal studies showed no deleterious effects of the drug treatment on anastomotic leaks.[107,108] In our own clinical trials described previously, no drug-related adverse events were noted, although only 34 patients were treated with the drugs. Also, the drug regimen that we have chosen takes into account the aforementioned recommendations and is based on effective standard doses used for other indications for propranolol and etodolac (eg, pain, anxiety, and hypertension). For a detailed discussion of safety concerns, please see the supporting information in Shaashua et al.[68]

Overall, preclinical and clinical evidence suggests that combined pharmacological inhibition of perioperative SIRs is superior to a separate blockade of either sympathetic responses or COX2 activity and may be necessary to effectively abolish the deleterious, prometastatic effects of perioperative SIRs.

PSYCHOPHYSIOLOGICAL INTERVENTIONS

Need for Perioperative Psychobehavioral Interventions

Surgery, especially oncological surgery, is perceived by most people as a stressful event.[32,109] While waiting for surgery, most people feel confusion, fear of the unknown, a lack of control, helplessness, and demoralization,[110-112] all of which can induce and increase stress or reduce a patient's capacity for coping with stress. As described previously, CAs secreted during stress also potentiate inflammation; thus, psychological stress can be expected to affect prometastatic pathways, including the cAMP-PKA pathway activated through adrenergic or prostanoid receptors. Hence, reducing psychological perioperative stress can be hypothesized to reduce postsurgical metastasis. There are at least 3 reasons for the need to reduce such responses through psychophysiological interventions rather than or in addition to pharmacological interventions. First, our recent experience with BC and CRC patients indicates that most patients have medical contraindications for the use of β-blockers and/or COX2 inhibitors, so alternative approaches should be considered.[12] Notably, it is possible that some of these contraindications could be weighed against the benefits of this drug regimen if this is indicated by large clinical trials. Nevertheless, some medical conditions may categorically prevent patients from receiving this treatment. These patients will require other forms of treatment. Second, although the combined perioperative use of propranolol and etodolac was effective in eliminating some preoperative stress responses, it did not prevent other responses, including increased cortisol and IL-10 levels before surgery.[68,113] A psychophysiological intervention may counteract aspects of the perioperative SIRs that are not inhibited by the pharmacological approach. Third, psychophysiological techniques could be practiced or could maintain their beneficial effects for an extended period and thus counteract SIRs for months or even years after surgery alongside a variety of cancer treatments and personal hardships.

Existing Perioperative Interventions

Existing preoperative or perioperative interventions can be classified into 3 main categories according to the focus of the intervention:

1. Psychoeducation: Because presurgical anxiety may stem from uncertainty regarding anticipated medical procedures, patients can benefit from information about surgical procedures, treatments, expected side effects, recovery processes, and so forth. Such information can be provided through written materials (brochures) or videos but is commonly more effective when it is communicated personally by the medical staff.[114,115]
2. Cognitive interventions: Ruminating thoughts, beliefs, and other cognitive processes before surgery are prevalent and are known to affect perioperative stress responses. Thus, cognitive interventions before surgery are directed at controlling the cognitive processes that evoke stress.[116,117]
3. Psychophysiological interventions: Most patients exhibit physiological reactions while anticipating surgery. These include high blood pressure, gastric perturbations, sleep disturbances, and muscle tension.[118-120] Relaxation, biofeedback, and hypnosis are often used to

alleviate these symptoms by reducing physiological responses and consequently reducing perceived stress. Hypnosis before breast biopsy was found to decrease postsurgical pain and distress.[121,122]

Importantly, adopting individualized preoperative interventions to the unique characteristics of each patient and his or her coping style has been shown by several studies to be more effective than fit-all standard interventions.[123-125] For example, some patients have the need to understand and choose specific medical procedures, whereas others prefer to be uninvolved.[126,127]

Why Are Perioperative Psychophysiological Interventions Not a Medical Routine?

Psychological interventions for cancer patients were found to be effective in improving both their psychological status and their immunological status.[128,129] However, only a few studies have reported long-term cancer outcomes of psychological interventions[13] despite decades of attempts, with some reporting positive survival outcomes,[124,130-134] whereas others have not.[135-139] Hence, it is not clear whether such interventions can indeed affect long-term cancer outcomes. We hypothesize that the scarcity of positive impacts of psychological interventions on long-term cancer outcomes is due to several reasons. These reasons include the following: 1) the intervention is initiated weeks or months after surgery rather than before it, so the critical perioperative period is not addressed; 2) there is a large variance in individuals' modes of stress responses, which are less likely to be addressed with the common group therapy approach; and 3) there is a need for pharmacological treatments during surgery to overcome the impact of tissue damage and other intraoperative procedures that may mask the beneficial effects of stress-reducing psychophysiological interventions.

Pilot Study of an Integrated, Tailored Perioperative Psychophysiological Approach

We are currently engaging in studying the effect of a psychophysiological intervention in BC patients, which will start approximately 3 weeks before surgery (on the preoperative preparation day) and will last until pathology results are reported to the patient (approximately 3 weeks postoperatively).[140] The intervention will include 3 to 5 face-to-face meetings with a psychologist as well as biweekly phone calls during which the various stressors that each woman confronts will be addressed in an individualized manner. In addition, patients without contraindications to propranolol and etodolac will be treated either with these medications or with a placebo (for 11 perioperative days beginning 5 days before surgery); this will test the efficacy of the aforementioned psychophysiological interventions with and without a pharmacological perioperative approach. It is hoped that beyond the improvement in women's well-being, the immediate and long-lasting stress-reducing effects of such a psychophysiological intervention may improve cancer outcomes.

In conclusion, we have found that

- The short perioperative period is critical in determining long-term cancer outcomes but rarely is exploited for antimetastatic therapy.
- Within the perioperative timeframe, stress and inflammatory responses synergistically promote metastasis, which accounts for the great majority of cancer-related deaths.
- On the basis of ample translational studies and recent clinical trials, the combined perioperative pharmacological blockade of β-adrenergic and COX2 signaling and/or alternative stress-reducing psychophysiological interventions seem promising for improving long-term cancer outcomes.
- These stress and inflammation–reducing interventions could transform the perioperative timeframe from being a catalyst of metastatic progression to an opportunity for arresting and/or eliminating residual disease, potentially saving patients' lives through the use of safe and inexpensive treatments.

FUNDING SUPPORT

This work was supported by National Cancer Institute/National Institutes of Health grants (CA125456 and CA172138 to Shamgar Ben-Eliyahu).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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