A New Approach to Reducing Postsurgical Cancer Recurrence: Perioperative Targeting of Catecholamines and Prostaglandins

Elad Neeman1, Oded Zmora2, and Shamgar Ben-Eliyahu1

Abstract

Surgery is a crucial intervention in most cancer patients, but the perioperative period is characterized by increased risks for future outbreak of preexisting micrometastases and the initiation of new metastases—the major cause of cancer-related death. Here we argue that the short perioperative period is disproportionately critical in determining long-term recurrence rates, discuss the various underlying risk factors that act synergistically during this period, and assert that this time frame presents an unexplored opportunity to reduce long-term cancer recurrence. We then address physiologic mechanisms that underlie these risk factors, focusing on excess perioperative release of catecholamines and prostaglandins, which were recently shown to be prominent in facilitating cancer recurrence through their direct impact on the malignant tissue and its microenvironment, and through suppressing antimetastatic immunity. The involvement of the immune system is further discussed in light of accumulating evidence in cancer patients, and given the recent identification of endogenously activated unique leukocyte populations which, if not suppressed, can destroy autologous “immune-resistant” tumor cells. We then review animal studies and human correlative findings, suggesting the efficacy of blocking catecholamines and/or prostaglandins perioperatively, limiting metastasis and increasing survival rates. Finally, we propose a specific perioperative pharmacologic intervention in cancer patients, based on simultaneous β-adrenergic blockade and COX-2 inhibition, and discuss specific considerations for its application in clinical trials, including our approved protocol. In sum, we herein present the rationale for a new approach to reduce long-term cancer recurrence by using a relatively safe, brief, and inexpensive intervention during the perioperative period.

The Brief Perioperative Period Is Disproportionately Critical for Determining Long-term Cancer Recurrence and Presents an Unexplored Opportunity for Effective Interventions

Surgical excision of the primary tumor has been suspected to facilitate the progression of preexisting micrometastases and the initiation of new metastases through several mechanisms, some of which have only recently been identified. Specifically, the unavoidable damage to the patients’ tissue and the manipulations and excision of the primary tumor and its vascularization were shown: (i) to increase shedding of tumor cells into the blood and lymphatic circulations (1); (ii) to naturally increase levels of growth factors that also act locally and systemically to facilitate the growth of minimal residual disease (2); and (iii) to decrease systemic levels of antiangiogenic factors (e.g., endostatin) due to the removal of the primary tumor that induced their release (3), thus shifting the anti-/proangiogenic balance in metastatic foci toward proangiogenesis.

In addition, numerous soluble factors increase systemically during the perioperative period as a result of patients’ neuroendocrine and paracrine responses to (i) the presence of the primary tumor; (ii) physiologic and psychologic stress; and (iii) the surgical procedure itself and its accompanying anesthesia, analgesia, blood transfusion, and other intraoperative procedures. These soluble compounds include catecholamines, prostaglandins, glucocorticoids, opioids, and a variety of administered anesthetic and analgesic agents. In recent years, it has become clear that in vitro, many of these factors act directly on malignant cells, activating several molecular processes that are critical for tumor metastatic activity, including tumor cell proliferation (4, 5), adhesion (6), locomotion (7), extracellular matrix invasion capacity (4), resistance to apoptosis and anoikis (8–10), and secretion of proangiogenic factors (11–13). In addition, in vitro and human and animal in vivo studies...
show that many of these soluble factors lead to suppression of antimetastatic cell-mediated immunity (CMI; refs. 14–16), which is indeed a common perioperative phenomenon (17–21). As will be elaborated below, this suppression may significantly promote long-term cancer recurrence.

Most importantly, all of the above prometastatic processes occur simultaneously during the brief perioperative period and thus may have a synergistic impact in promoting long-term cancer recurrence. For example, the drop in antiangiogenic compounds, simultaneously with the rise in growth factors and in proangiogenic factors released by malignant and injured tissue, may turn on the angiogenic switch, causing dormant metastatic foci to initiate their growth (22). Simultaneously, excess release of malignant cells into the blood or lymphatic circulation, combined with suppressed antimetastatic immunity, may render the patient markedly susceptible to metastatic dissemination and outbreak—a process that could have been prevented if such multiple deleterious processes had not been initiated (Fig. 1).

On the other hand, were it possible to circumvent at least some of these deleterious processes, the perioperative period would then theoretically also present an opportunity to eradicate cancer or successfully arrest its progression. Specifically, removal of the primary tumor reduces the potential immunosuppressive effects of the large malignant mass and its microenvironment (23) and eliminates the ongoing release of metastasizing malignant cells. Minimal residual disease is apparently more easily controlled than the primary tumor and may thus be eliminated by a now more effective CMI.

**Translational Relevance**

Metastasis is the common cause of morbidity and death in cancer patients. Ample evidence from animal and human studies has long indicated that surgery and other perioperative processes can promote metastasis. Recent research has identified several underlying perioperative neuroendocrine mediators, of which excess catecholamines and prostaglandins play a pivotal role. These compounds can act directly by stimulating prometastatic capacities of the malignant tissue and its microenvironment, and/or through suppressing cell-mediated immunity. Recent animal studies targeting catecholamines, prostaglandins, or both, in the perioperative context, have shown reduced metastasis and increased survival rates, and human correlational findings were consistent with these outcomes. Here we discuss and analyze findings from different fields of study suggesting the above mediating mechanisms and supporting the rationale for a brief perioperative clinical intervention simultaneously targeting catecholamines and prostaglandins. We conclude by suggesting specific considerations for randomized controlled trials in cancer patients aimed at reducing recurrence rates through this intervention.

**Excess Perioperative Catecholamines and Prostaglandins Are the Key Factors in Promoting Tumor Metastasis by Directly Impacting the Malignant Tissue and by Suppressing Antimetastatic CMI**

Catecholamine and prostaglandin levels are commonly elevated perioperatively. Many tumors release prostaglandins, or recruit macrophages to do so (23), presumably as an immune-escape mechanism or to promote tumor vascularization. Catecholamines are abundantly released throughout the perioperative period, because of the patient’s anxiety and fear of the disease, the medical procedures, cancer recurrence, and death. In addition, tissue damage directly induces the local release of prostaglandins (24), and catecholamine secretion is a prominent neuroendocrine response to tissue damage and its accompanied inflammation, nociception, and pain (25). Interestingly, many human malignancies express receptors for catecholamines (26) and prostaglandins (27), and almost all leukocytes express both receptor systems (28, 29). Thus, it is reasonable to assume that both immune and tumor cells are affected by catecholamines and prostaglandins, which are simultaneously elevated during the perioperative period (17).

Indeed, catecholamines were recently shown to directly act on human and animal malignant cells, changing their cellular characteristics to those favoring metastatic spread and growth. Specifically, in vitro and animal in vivo studies using a variety of human tumor lines indicated that activation of tumor β-adrenoceptors can (i) enhance the production of several metastasis-promoting factors by tumor cells, including VEGF, matrix metalloproteinase 2 (MMP-2), and MMP-9, interleukin 6 (IL-6), and IL-8, and (ii) facilitate tumor angiogenesis, survival, migration, proliferation, and resistance to anoikis—effects that were all blocked by β-antagonists (5, 7, 10, 11, 13, 30, 31). In addition, blockade of β-adrenergic receptors was shown to induce apoptosis of several human and animal carcinoma cell lines (32, 33). Similarly, prostaglandins were repeatedly implicated in promoting neoplastic progression in human and animal in vivo and in vivo studies. Prostaglandin-E2 (PGE2) administration was shown to facilitate macrophage differentiation toward the protumoral M2 phenotype, contributing to cervical carcinoma tumor angiogenesis (34). In colorectal cancer patients, tumor COX-2 expression levels were associated with tumor size, stage, blood vascularization, depth of invasion, lymph node metastasis, recurrence, and overall survival rates (35). Blocking the COX-2 pathway in patients or animals was shown to promote tumor cell apoptosis (9, 36), to reduce levels of proangiogenic agents (12), and to decrease tumor microvascular density (9).

In addition to their aforementioned direct effects, both catecholamines and prostaglandins have been repeatedly shown in vitro to suppress most aspects of CMI, including CTL, macrophage, dendritic, and natural killer (NK) cell activity (37–41). These effects are mainly mediated through activation of leukocyte membrane receptors for these ligands and intracellular initiation of the cAMP-PKA...
Immunosuppression and direct effects on malignant tissue

**Circulating tumor cell in lung**
- MP-NK
- Alveolus

**Preexisting liver micrometastasis**
- Liver sinusoid
- NKT-1
- Pit

**Suppression of antimetastatic CMI**
- CTL cytotoxicity ↓
- NK cytotoxicity ↓
- TRAIL, FAS, NKG2D ↓
- Unique leukocyte populations:
  - MP-NK, NKT-1, pit cell cytotoxicity ↓
- Dendritic cell maturation ↓
- Th1/Th2 ratio ↓
- M2 macrophage differentiation ↑

Direct effects on malignant tissue
- Tumor cell proliferation ↑
- Tumor cell motility ↑
- Tumor cell invasion capacity ↑
  - MMP-2, MMP-9 ↑
- Tumor cell resistance to apoptosis ↑
- Secretion of proangiogenics ↑

Risk factors of the perioperative period

**Central nervous system**
- Activation of SNS
- Catecholamines ↑
- Activation of HPA axis
- ACTH ↑
- Opioids ↑
- Hypothermia

**Adrenal glands**
- Medulla
- Catecholamines ↑
- Opioids ↑
- Cortex
- Glucocorticoids ↑

**I.v. administration**
- Analgesics and anesthetics
- Blood transfusion

**Resection of the primary tumor**
- Tumor cell shedding ↑
- Prostaglandins ↑
- Growth factors ↑
- Proangiogenics (e.g., VEGF) ↑
- Antiangiogenics (e.g., endostatin) ↓

Unique leukocyte populations: MP-NK, NKT-1, pit cell cytotoxicity ↓
- Dendritic cell maturation ↓
- Th1/Th2 ratio ↓
- M2 macrophage differentiation ↑

Figure 1. Risk factors and processes occurring during the perioperative period, facilitating metastatic progression. Risk factors that characterize the perioperative period, including those associated with resection of the primary tumor and the neuroendocrine responses to stress and surgery, are shown on the right side of this figure. As shown on the left side of this figure, these risk factors exert deleterious effects on cell-mediated antimetastatic immunity and directly promote progression of residual malignant tissue, including circulating tumor cells and preexisting micrometastases. ACTH, adrenocorticotropic hormone; HPA, hypothalamic–pituitary–adrenal; MP, marginating pulmonary; NKT, natural killer T cell; SNS, sympathetic nervous system.

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cascade common to both receptor systems (42, 43). Catecholamines and prostaglandins are also known to shift the Th1/Th2 cytokine balance toward anti-CMI Th2 dominance (15, 16) and to increase adrenocorticotropin hormone and glucocorticoid levels (44), potentially suppressing additional aspects of CMI through these responses. Our in vivo animal studies indicated that administration of catecholamines (45, 46) or prostaglandins (47), or exposure to behavioral stress and activation of the sympathetic nervous system (48), can each suppress NK activity in vivo; in addition, our findings show that this immune suppression can compromise resistance to experimental metastasis (46–47) and to leukemia progression (14). Therefore, surgery-related responses can potentially promote the metastatic process through the release of catecholamines and prostaglandins, which can act directly on the malignant tissue and its microenvironment and simultaneously suppress antimetastatic CMI (Fig. 1). Indeed, animal studies indicated that the use of a β-adrenergic blocker or a COX-2 inhibitor attenuated or abrogated the tumor-promoting effects of surgery, which were mediated through suppression of NK activity (19, 20, 49) and through other mechanisms (50), including direct effects on the malignancies (51). Furthermore, in 2 models of spontaneous metastasis, in which a primary orthotopic metastasizing tumor was removed surgically, the simultaneous blockade of the 2 factors doubled long-term survival rates. It is noteworthy that, the blockade of any of these factors alone did not increase survival rates (20), nor did it prevent postoperative suppression of NK activity (19). We believe that the inefficiency of each blocker alone is ascribed to the fact that catecholamines and prostaglandins are simultaneously elevated during the perioperative period, causing redundant effects of these factors on immunocytes and on malignant cells.

In sum, we believe that catecholamines and prostaglandins are key mediators of the harmful effects of surgery on metastatic progression, as they (i) directly impact cells of the immune system and of the malignant tissue as detailed above, and (ii) induce other humoral responses that have similar effects on immunocytes and malignant tissue, including proinflammatory responses, activation of the hypothalamic–pituitary–adrenal axis, and the shift toward Th2 cytokine dominance. The notion that excess perioperative catecholamine and prostaglandin seclusions in cancer patients may increase long-term recurrence rates warrants the study of pharmacologic interventions targeting these compounds (see below); in addition, it supports the claim that adequate anxiety and pain control in this context may have beneficial effects on cancer prognosis.

New Evidence for the Significance of Antimetastatic Immunity in the Perioperative Context

The claim that suppression of CMI promotes the metastatic process relies on the assumption that CMI encompasses antimetastatic capacities. Animal studies provided ample evidence supporting this immune-surveillance hypothesis but were justifiably criticized for not simulating many aspects of human cancer progression (17). However, evidence from cancer patients clearly indicates that the immune system extensively interacts with developing primary tumors, metastasizing cells, and established metastases, recognizing and killing many malignant cells, but eventually sparing tumor foci that have adopted efficient immune-escape mechanisms—a process that is now termed “immunoediting” (52). Attesting to these processes in cancer patients and to the significance of immunosuppression are the numerous immune-escape mechanisms revealed in human malignancies (23); the finding that in vitro mixed lymphocyte response against excised autologous breast tumors predicts long-term survival rates better than tumor stage and grade (53); the increased frequency of certain malignancies and the dramatic rise in metastatic development in immunocompromised patients of various etiologies (54, 55); and the recent promising outcomes of immune-based therapies, including the CTLA-4 receptor blocker ipilimumab, which enhances T-cell–mediated anti-tumor immunity and increases survival (56).

Importantly, several new leukocyte populations that were recently identified in vivo in rodents, and some also in humans, exhibit a unique ability to kill autologous tumor cells that were traditionally considered immune resistant. These populations include type-1 natural killer T cells (57); marginating pulmonary leukocytes and their subpopulation of activated NK cells (49, 58); liver pit cells, which are activated NK cells residing in hepatic sinusoids (59); dendritic epidermal T cells (60); and killer dendritic cells (ref. 61; Fig. 1). These populations resemble in vitro activated lymphocytes in terms of their cytotoxic activity and gene expression profile but exist endogenously without immune stimulation. In addition, most of these populations are strategically located in capillaries or other structures that filter all circulating blood and foster close contacts with circulating malignant cells, enabling efficient recognition and destruction of aberrant cells. Finally, most of these unique leukocyte populations have already been shown to be suppressed by catecholamines and/or prostaglandins, including marginating pulmonary leukocytes (19, 49, 62, 63), type 1 natural killer T cells (64), and dendritic epidermal T cells (65).

Blockade of Catecholamines or Prostaglandins during the Perioperative Period in Cancer Patients

COX-2 inhibitors have been extensively studied as long-term chemopreventers of numerous malignancies (e.g., gastrointestinal tract, breast, and skin tumors) and showed promising outcomes (66). However, this chronic approach focuses on prophylaxis and uses minimal doses, which cannot be expected to effectively antagonize the massive release of prostaglandins in the perioperative context. Similarly, a few epidemiologic studies have also examined the impact of a chronic use of β-blockers on breast cancer initiation and progression and indicated a modest but significant reduction in cancer rates (67, 68).
To this day, only a few randomized controlled trials (RCT) or retrospective cohort studies have examined the impact of a focused acute perioperative treatment with either a β-blocker or a COX inhibitor on long-term cancer outcomes. Specifically, in gastric or esophageal cancer patients, a very low daily dose of aspirin (25–50 mg/d) during the first postoperative year significantly improved the 5-year survival rate from 41% to 51.2%, but only in low-stage, nondisseminated malignancies (T2N0M0; ref. 69). In addition, 3 RCTs studied the effects of a 2- to 4-week presurgical treatment with 400 to 800 mg/d of the COX-2 inhibitor celecoxib on tumor characteristics in patients with stage I/II primary breast cancer (70), invasive transitional cell carcinoma (71), or prostate cancer (72). The first 2 studies exhibited a modest increase in tumor cell apoptosis; the last study also indicated a reduction in tumor cell proliferation, microvessel density, angiogenesis, and hypoxia-inducible factor-1α expression.

We could not locate any RCT that had directly tested the impact of perioperative treatment with a β-blocker on long-term survival. However, several retrospective epidemiologic studies had found associations between these variables. Specifically, in triple-negative breast cancer patients, the use of β-blockers for several months before surgery, along with neoadjuvant therapy, was associated with an improved recurrence-free survival (73); moreover, in malignant melanoma patients, a β-blocker treatment significantly predicted a reduced cancer-related and all-cause mortality, even when initiated less than 90 days before diagnosis and surgery. Interestingly, and similarly to other studies described above, the β-adrenergic blockade was effective only in nonmetastasized (stage I/II) melanomas (74). This suggests that the treatment is effective in controlling the initial stages of the metastatic process, rather than established malignant foci.

The above human studies present only initial indications for positive effects of β-blockers or of COX inhibitors in the context of oncologic surgery. To date, no study had used a combined perioperative regimen of β-blockers and COX inhibitors in cancer patients. Considering the common intracellular pathways that are activated by membrane receptors for catecholamines and prostaglandins (42, 43), and the simultaneous excess release of both factors during the perioperative period, it is reasonable that only a combined blockade during this critical time frame could result in a substantial improvement in long-term recurrence-free survival. In our animal studies, we directly compared each drug alone to a combined use and found the combined treatment to be either significantly more effective or the only effective intervention in increasing survival rates in mice undergoing excision of a spontaneously metastasizing primary tumor (20).

Rationale and Specific Considerations for RCTs Testing a Perioperative Blockade of Catecholamines and Prostaglandins in Cancer Patients

We believe that cancer patients will benefit from a brief perioperative treatment that is based on a β-blocker and a COX-2 inhibitor, given (i) the disproportional impact of the short perioperative period in determining long-term cancer outcomes; (ii) the recent discovery of leukocyte populations that can control tumor progression and provide protection from immunosuppression; (iii) the recent findings that excess catecholamine and prostaglandin secretions underlie many of the perioperative risk factors for long-term recurrence, through immune suppression and through nonimmunologic mechanisms; and (iv) the few positive findings in animal and human studies using each drug alone (69–74), and the promising results from our animal studies using the combined blockade of catecholamines and prostaglandins (19, 20). To the best of our knowledge, this new approach for reducing cancer recurrence has never been clinically tested in cancer patients. Therefore, we hereby propose specific considerations for such RCTs.

Drug schedule

We propose to test a 2- to 4-week perioperative treatment with a combination of a nonselective β-adrenergic blocker (e.g., propranolol) and a selective COX-2 inhibitor (e.g., etodolac), beginning a few days before surgery. Based on the suggested synergistic impact of propranolol and etodolac, we do not recommend testing each of these drugs separately without testing their combination. Both drugs are in routine clinical use and are not reciprocally contraindicated; accordingly, we propose simultaneous intermediate doses that are considered safe and effective for other indications (e.g., pain and hypertension). To reduce potential adverse effects, propranolol should be given at escalating, peak, and withdrawal doses, ranging from 40 to 160 (or more) mg/d (peaking on the day of surgery). Propranolol is preferred over selective β1-blockers, as immunocytes predominantly express β2 over β1 adrenoceptors, and both have been implicated in immune suppression (45, 75, 76). In low doses, propranolol is also anxiolytic (77). Etodolac should be given at a dose of 600 to 1,200 mg/d. Etodolac is preferred over other COX inhibitors, given its relative selectivity toward COX-2 inhibition (78) and few known side effects compared with more selective COX-2 inhibitors.

The drug treatment should commence a few days before surgery, as psychologic distress and malignant tissue (and its surrounding stromal and immune cells) are known to induce the release of catecholamines and prostaglandins, respectively, even before surgery when immune suppression has been reported (18, 21). It may be paradoxically destructive to initiate drug treatment long before surgery, as enhancing immune antitumor activity without tumor removal may theoretically cause harmful immunoediting, selecting immune-resistant tumor cells. Drug treatment should be terminated approximately 1 to 3 weeks postoperatively, as we expect major immune and endocrine perturbations to dissipate by this time (21, 79) and as adverse effects of COX inhibitors accumulate over time.

Patients

We recommend that only patients with a single operable tumor without apparent metastatic disease will be included
in such an RCT. We also recommend excluding patients with a history of previous malignancies, patients in whom surgical resection is planned without curative intent, and patients with contraindications for these drugs (e.g., cardiac conduction defects or renal failure).

Cancer type and surgery type
All cancers with the potential to metastasize could be considered for this kind of RCT. Although it may be hypothesized that more extensive surgeries would bear greater deleterious consequences, this notion has been ascertained only with respect to some immunologic indices and less so with respect to tumor progression and survival rates (80), including in colorectal cancer patients (81). Our animal studies indicated that adding a laparotomy to a minor surgery did not significantly increase long-term mortality rates, and that the proposed drug intervention was similarly effective in minor and more severe procedures (20). These findings suggested that cancer patients undergoing minor or major surgeries might all benefit from the treatment.

Outcomes
The primary outcomes of such a potential RCT should include long-term cancer recurrence, cancer-related mortality, and all-cause mortality. Secondary/interim outcomes could include (i) pre- and postsurgical immune indices, including a complete differential blood count, NK cytotoxicity, and pro- and anti-inflammatory cytokine levels (e.g., IL-6, IL-12, and IFN-γ); (ii) pre- and postsurgical general markers of angiogenesis, tumor invasion, and surgical stress responses such as plasma levels of VEGF, soluble VEGF receptor 1, MMP-2, MMP-9, cortisol, and C-reactive protein; (iii) postexcisional histologic tumor expression levels of prometastatic compounds (e.g., VEGF, PGE2) and tumor receptors for catecholamines, prostaglandins, and growth factors; and (iv) post-surgical complications and daily amounts of morphine and other narcotics used over the postoperative period. We hypothesize that the primary and most interim outcomes will be improved in the experimental group, and that, as suggested by the literature, the interim measures will predict long-term outcome and will suggest specific underlying mechanisms.

In conclusion, we herein present and rationalize a new approach to reducing long-term cancer recurrence in patients through studying the use of a brief pharmacologic intervention to mitigate excess perioperative effects of catecholamines and prostaglandins. This unexplored approach is also advantageous in that it uses commonly administered medications that are relatively safe, accessible, and inexpensive.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions
Conception and design: E. Neeman, O. Zmora, S. Ben-Eliyahu
Development of methodology: O. Zmora
Writing, review, and/or revision of the manuscript: E. Neeman, O. Zmora, S. Ben-Eliyahu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. Neeman, S. Ben-Eliyahu
Study supervision: S. Ben-Eliyahu

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