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Exploiting the critical perioperative period to improve long-term cancer outcomes

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Abstract

Evidence suggests that the perioperative period and the excision of the primary tumour can promote the development of metastases—the main cause of cancer-related mortality. This Review first presents the assertion that the perioperative timeframe is pivotal in determining long-term cancer outcomes, disproportionally to its short duration (days to weeks). We then analyse the various aspects of surgery, and their consequent paracrine and neuroendocrine responses, which could facilitate the metastatic process by directly affecting malignant tissues, and/or through indirect pathways, such as immunological perturbations. We address the influences of surgery-related anxiety and stress, nutritional status, anaesthetics and analgesics, hypothermia, blood transfusion, tissue damage, and levels of sex hormones, and point at some as probable deleterious factors. Through understanding these processes and reviewing empirical evidence, we provide suggestions for potential new perioperative approaches and interventions aimed at attenuating deleterious processes and ultimately improving treatment outcomes. Specifically, we highlight excess perioperative release of catecholamines and prostaglandins as key deleterious mediators of surgery, and we recommend blockade of these responses during the perioperative period, as well as other low-risk, low-cost interventions. The measures described in this Review could transform the perioperative timeframe from a prominent facilitator of metastatic progression, to a window of opportunity for arresting and/or eliminating residual disease, potentially improving long-term survival rates in patients with cancer.

Introduction

The perioperative period—days before to days–weeks following tumour excision—is short relative to the time-span of primary tumour evolvement, or even relative to the timeframe of the metastatic process. Nevertheless, several studies have reported that this short period is critical in determining the risk of postoperative metastatic disease.[1–3] Although surgeons usually achieve negative margins when excising a primary tumour, there is a high risk of

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M.H. and E.N. researched data for article. All authors provided substantial contribution to discussion of content, reviewed and edited the manuscript before submission. M.H., E.N. and S.B.-E. wrote the manuscript.

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residual malignant cells and patients are often treated for potential residual disease (commonly using chemotherapy). Residual tumour cells might be present proximal to the excision location, in the lymphatic system (within positive lymph nodes) or blood circulation, or in distal organs, in the form of single tumour cells or as micrometastases.

Importantly, although surgical excision of a primary solid tumour is crucial and life-saving, the procedure can also facilitate the development of metastases from these residual malignant cells through numerous mechanisms (Figure 1). The unavoidable damage to the patients' tissues, and the excision and manipulations of the primary tumour and its vasculature during surgery have been shown to increase shedding of tumour cells into the blood and lymphatic circulations,[4] to increase local and systemic levels of growth factors,[5] and to decrease systemic levels of primary-tumour-associated anti angiogenic factors (such as endostatin).[6,7] Moreover, the patients' paracrine and neuroendocrine responses to surgery, including the release of prostaglandins and catecholamines, can act directly on the primary tumour and residual malignant cells, facilitating malignant cell survival, motility, invasion, proliferation and release of proangiogenic factors,[8] suppress antimetastatic immunity,[2] and fertilize the microenvironment of residual malignant cells.[9]

These pro-metastatic processes occur simultaneously during the short perioperative period, potentially making this timeframe critical in determining the oncological outcome. Specifically, it is the synchronization and synergism between these deleterious processes that theoretically renders the patient exceptionally susceptible to a metastatic disease.[2] For example, increased numbers of circulating malignant cells, combined with more-aggressive and pro-metastatic characteristics of such cells and suppressed antimetastatic cell-mediated immunity, could enable these tumour cells to establish metastases in distal organs. Additionally, reduced expression of antiangiogenic factors, alongside surgery-induced increases in the levels of growth factors and of proangiogenic compounds, might enable undetectable dormant metastases to undergo the angiogenic switch and quickly grow beyond a critical mass that cannot be controlled.

However, if one can arrest these perioperative prometastatic processes, then the immediate postoperative period would also become a unique window of opportunity to eradicate and/or control residual malignant cells before they adopt characteristics of the former primary tumour, and therefore grow and spread around the body. Specifically, removal of the major bulk of the primary tumour terminates the proinflammatory and/or immunosuppressive effects of many primary tumours,[10] and blocks the ongoing release of malignant cells into the blood and lymphatic circulation. Under such improved conditions, single tumour cells and micrometastases are more easily controlled by cell-mediated-immunity (CMI) than were the primary tumour and the metastatic process,[2] enabling the last residual malignant cells to be eliminated or maintained in a dormant state.

On this basis, the perioperative period should be exploited to reduce metastatic progression and/or to improve oncological outcomes.[1,11–13] This period has been relatively unexplored therapeutically, because traditional chemotherapies and radiation therapies cannot be used during this period, given their suppressive effects on the immune system and/or tissue

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healing. However, as we discuss in this Review, various other interventions are feasible during this perioperative timeframe, and some hold great promise.

Perioperative physiological responses

The term surgical stress is widely used to describe the hormonal and metabolic changes that follow injury or trauma, including activation of the sympathetic nervous system, the endocrine (corticosteroids) 'stress response', and the con sequent immunological and haematological changes.[14] Herein, we address not only these responses, but also several additional biological factors that are altered during the perioperative period and have been shown to impact long-term oncological outcomes.

Specifically, tumour excision initiates a cascade of biological perturbations, including local, cellular and neuronal responses, as well as paracrine and endocrine alterations.[15] In addition, environmental challenges that affect the patient in the perioperative timeframe, such as psychological distress, intraoperative hypothermia and administration of anaesthetic agents or blood products, also trigger a variety of physiological responses that can substantially affect the metastatic process, through effects on distal malignant cells, their microenvironment, and the interacting immunocytes (Figure 1).

A key role for catecholamines and prostaglandins

Catecholamine and prostaglandin levels are commonly increased perioperatively. Catecholamines are abundantly released due to the patients' anxiety and fear of the disease and the medical procedures. Tissue damage directly induces the local release of prostaglandins,[16] and catecholamine secretion is a prominent neuroendocrine response to tissue damage and the related inflammation, nociception, and pain.[17] Many tumours also release prostaglandins, or recruit macrophages that do so,[10] presumably to promote tumour vascularization or to suppress immune recognition and destruction. Other soluble factors are also elevated systematically in the perioperative period, including glucocorticoids and opioids.[18] However, their independent role in promoting metastasis seems less consistent.[19]

The direct effects of catecholamines and prostaglandins on malignant tissue have only recently been acknowledged. Many human malignancies express receptors for catecholamines[20] and prostaglandins,[21] and their activation can promote the metastatic potential of the tumour through several molecular mechanisms, including the promotion of tumour-cell proliferation,[22,23] adhesion,[24] locomotion,[25] extracellular matrix invasion,[22] resistance to apoptosis and anoikis,[26–28] and secretion of proangiogenic factors such as vascular endothelial growth factor (VEGF).[29–31] These processes are critical for the metastatic dissemination and growth of malignant tissue; thus, attenuating them might preclude metastatic outbreak.

The indirect effects of catecholamines and prostaglandins are mediated through various mechanisms, including the perioperative suppression of antimetastatic immunity (see 'Immunosuppression and cancer recurrence' section),[15,18,32–37] tumour-promoting alterations in the microenvironment of the residual malignant cells,[8] and potential

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stimulation of lymphatic-mediated spread of malignant cells (Sloan, E. personal communication).

Immunosuppression and cancer recurrence

The claim that suppression of CMI promotes the metastatic process relies on the assumption that CMI—for example, cytotoxicity mediated by natural killer (NK) cell or cytotoxic T lymphocyte (CTL)—encompasses antimetastatic capacities. Studies performed in animal models provide unequivocal evidence in support of such a role for various immunocytes, including CTLs, NK cells, macro phages, and dendritic cells.[15] For example, NK cells are able to identify and kill malignant cells, inducing apoptosis through the perforine-granzyme and death-receptor pathways.[38] Accordingly, rodents with a deficient NK-cell system develop more tumours and metastases than do naive animals,[39–41] and rats in which NK cells were depleted showed greater lung retention of syngeneic cancerous cells (following their intra venous administration) and increased numbers of metastatic foci.[42–44] Importantly, almost all leukocytes express receptors for catecholamines and prostaglandins,[45,46] and similar to most other aspects of CMI, NK cells are directly inhibited by catecholamines and prostaglandins;[47] this inhibition has been shown to exacerbate the metastatic process in animal models.[34,44]

In clinical studies in patients with cancer, which provide outcomes of a less causal nature compared with animal studies, but hold greater validity, ample evidence indicates an important role for CMI in controlling the metastatic process. Specifically, clinical studies have revealed that the immune system extensively interacts with developing primary tumours, metastasizing cells, and established metastases, leading to recognition and killing of many malignant cells, but eventually sparing tumour foci that have adopted effective immune-escape mechanisms—a process that is now termed ‘immunoediting’.[48] Attesting to these processes in patients with cancer, and to the significant deleterious consequences of immunosuppression are: the numerous immune-escape mechanisms revealed in human malignancies;[10] the finding that *in vitro* mixed lymphocyte response against excised autologous breast tumours predicts long-term survival rates better than tumour stage and grade;[49] the increased frequency of certain malignancies, and the dramatic increase in metastatic development in patients immunocompromised by various aetiologies (compared with patients with intact immune systems);[50,51] and the promising outcomes of FDA-approved immune-based therapies, including the cancer vaccine sipuleucel-T,[52] the CTLA-4 receptor blocker ipilimumab (which enhances T-cell mediated antitumour immunity and increases survival),[53] and anti-PD-1 and anti-PD-L1 antibodies with promising clinical activity in several tumour types.[54]

Recent findings further resolve prior reservations regarding the antimetastatic capacities of CMI. Several unique leukocyte populations were identified *in vivo*, in both rodents and humans, which had a remarkable ability to recognize and kill autologous tumour cells that were traditionally considered ‘immune-resistant’, including type-1 natural killer T (NKT) cells,[55] marginating-pulmonary leukocytes and their subpopulation of activated NK cells,[56,57] liver pit cells (activated NK cells in hepatic sinusoids),[58] dendritic epidermal T cells,[59] and killer-dendritic cells.[60] These cell populations resemble *in-vitro*-activated

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lymphocytes in terms of their heightened cytotoxic activity and gene-expression profile, but exist endogenously without immune stimulation.[2] Their capacity to kill autologous tumour cells far exceeds the capacity of traditionally studied circulating leukocytes.[2] Furthermore, most of these unique leukocytes are strategically located in capillaries of major organs (such as the lungs) that filter all circulating blood and foster close contacts with circulating malignant cells, thus enabling efficient recognition and destruction of these aberrant cells.[2] In addition, most of these unique leukocyte populations, including marginating-pulmonary leukocytes,[35,56,61,62] type-1 NKT cells,[63] and dendritic epidermal T cells,[64] have been shown to be suppressed by catecholamines and/or prostaglandins. Thus, all these studies clearly indicate that intact immunity is an important factor in controlling the metastatic process, bearing a greater role in this regard than previously assumed.[65]

Surgical aspects affecting recurrence

The perioperative period in patients undergoing oncological surgery is characterized by countless and varying factors; of note, each of these factors can alter oncological outcomes. In this Review we focus on those factors that are directly affected by surgery and/or by interventions or events occurring during the perioperative period. Even though pre-existing factors such as co-morbidities, performance status, and body mass index can influence oncological outcomes substantially,[66,67] they are beyond the scope of this Review.

Anaesthetic and analgesic approaches

The choice of anaesthetic and analgesic approach used during surgery and the perioperative period has long been proposed to influence cancer recurrence.[68] In general, it seems that both general anaesthesia and the use of considerable quantities of opioid analgesics often increase recurrence rates.[69] By contrast, efficient pain alleviation through the use of local or regional anaesthesia–analgesia, with or instead of general anaesthesia, might improve long-term cancer outcomes.[12,13] Unfortunately, the available evidence regarding the effects of specific anaesthetic and analgesic agents and techniques, as well as the mechanisms mediating their alleged effects on cancer outcomes, are inconclusive.[70–72] The question of whether regional anaesthesia–analgesia could indeed improve oncological outcomes remains unresolved, as none of the aforementioned studies that failed to support this hypothesis had the statistic power to detect effects smaller than a 33% improvement in recurrence-free survival. Furthermore, most studies addressing this issue were retrospective, and some had unavoidable methodological limitations, which potentially hindered their ability to pinpoint the effects of regional anaesthesia–analgesia. Several larger clinical trials are ongoing (NCT00684229, NCT00418457, NCT01179308),[73–75] and might yield more-definitive data.

Anaesthetic agents can directly influence the malignant tissue and its cellular microenvironment,[76] and can affect the neuroendocrine system and the immune system in complex manners; thus, it is likely that specific agents and approaches will have complex and potentially opposing effects, depending on circumstances,[77–79] and the choice of anaesthetic and analgesic approaches should be planned carefully in conjunction with other aspects of surgery, based on the following considerations.

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First, high doses of opiates have been mostly shown (in animals and/or humans) to activate stress responses, suppress antimetastatic CMI, increase angiogenesis, increase pro-metastatic characteristics of tumour cells, and promote progression of metastases.[76,78–81] Second, suppression of pain and nociception through the use of non-opiate agents, such as tramadol, cyclooxygenase (COX) inhibitors, or low doses of opiate drugs, such as fentanyl, has been demonstrated to reduce stress responses and sympathetic activity in patients, and seems to decrease metastasis in murine models.[82,83] Of note, the use of COX inhibition might be a crucial addition to such intervention, which could help to maximize the benefits in the context of tissue damage and residual malignant cells.[36] Third, the use of volatile and nonvolatile anaesthetics that activate the sympathetic nervous system and/or adrenergic receptors (for example, ketamine, but not propofol) has been associated with increased metastatic progression in rodents through stimulation of adrenergic responses.[78,84,85] Finally, regional anaesthesia and spinal blockade in patients with cancer efficiently reduce intraoperative and postoperative sympathetic responses, and were shown to either markedly improve long-term cancer outcomes,[12,13,86,87] or to have no effect,[70–72,86] but never to worsen outcomes.[68,88]

Therefore, until further evidence is obtained through dedicated clinical trials, when feasible it seems favourable to replace general anaesthesia and opiates with regional anaesthesia–analgesia, tramadol, and/or non-opiate analgesics, or to add regional anaesthesia–analgesia to general anaesthesia when operating on patients with cancer, while also ensuring adequate pain control.

Blood transfusion

Blood transfusion, often required during surgery, has been repeatedly shown to cause immunosuppression or immune perturbations[89] through increase in prostaglandin production[90] and other physiological alterations, which lead to suppression of NK activity[91] and inefficient immune reactivity or immune tolerance.[92] These physiological and immunological modulations were suggested to underlie the increase in cancer mortality rates associated with blood transfusion, which was reported in several types of cancer and repeatedly in colorectal cancer.[93] However, the medical circumstances that necessitate blood transfusion, rather than the procedure itself, could be the cause of the increased cancer mortality, as all clinical studies testing the effect of blood transfusion are naturally cohort studies (most are retrospective), as one cannot randomize patients to receive or not receive blood transfusion. To overcome this methodological obstacle, several studies incorporated designs that took into account all known potential con-founders (such as tumour stage and duration of surgery), and nevertheless reached the same conclusion in terms of cancer mortality—that is, that the transfusion has an independent deleterious influence.[94–96]

Of note, studies also indicated an advantage for specific transfusion protocols.[96] For example, the transfusion of packed red blood cells, rather than whole blood, was shown to minimize the deleterious effects of the transfusion[92] (also in a prospective study[91]), suggesting that transfused allogeneic leukocytes might constitute additional targets for the host’s immune system, a potential source of transfused blood-related immunosuppressive factors, and an additional cause for host perioperative stress responses. The number of blood

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units transfused has been unequivocally correlated with survival rates, even when adjusting for other risk factors.[97,98]

Beyond the specific constituents of the transfused blood, other factors, such as the storage of the blood cells, also have an impact on oncological outcomes. Indeed, it has been shown in rodents that the use of erythrocytes stored beyond nine days before transfusion increased susceptibility to various circulating malignant cells, whereas the storage interval of allogeneic leukocytes or their secreted factors had only a minor impact.[99] These un desirable effects of transfused erythrocytes were restricted to a short post-transfusion perioperative period, and can be explained by exhaustion of host antimetastatic immuno-cytes (such as NK cells) that are diverted and saturated by the countless transfused deteriorating erythrocytes.[99]

Overall, it seems advantageous to reduce the likelihood of a blood transfusion by using bloodless surgery techniques,[100,101] minimizing the number of blood units transfused, and/or using packed red cells instead of whole blood for the transfusion itself. The optimal storage interval of the transfused blood should be evaluated clinically.

Hypothermia

Mild perioperative hypothermia (up to a 2 °C decrease from the normal body temperature), which is commonly caused by surgery,[102] has immunosuppressive and other maladaptive consequences. For example, 24 h after surgery, hypothermia results in reduced production of IL-1β and IL-2, suppressed mitogen-induced lymphocyte proliferation, and elevated cortisol levels.[103] Furthermore, hypothermia also activates the sympathetic nervous system (SNS), leading to elevated noradrenaline levels,[104] and potentiates the requirement for blood transfusion, owing to impairment in platelet function and in the coagulation cascade.[105]

Overall, considering that hypothermia causes perturbations in various physiological indices and results in deleterious clinical outcomes,[106] it should also be suspected to worsen cancer prognosis. Indeed, in a rat model of colon cancer, tumour growth was increased by perioperative hypothermia,[107] and severe hypothermia (3–7 °C decrease from the normal body temperature) markedly suppressed NK-cell activity and jeopardized host resistance to experimental mammary metastasis, effects that were attenuated by β-adrenergic blockade.[85] However, no sufficiently powered clinical studies or randomized trials have been conducted to elucidate the influence of hypothermia on cancer recurrence.

Maintaining normothermia during surgery is, now-adays, mandatory in most medical centres; however in some hospitals at which such a requirement is not implemented, we recommend to strictly avoid hypothermia in patients undergoing tumour resection.

Laparoscopy, open surgery, and tissue damage

Numerous studies have indicated the beneficial effects of laparoscopy compared with open surgery on several short-term clinical outcomes in various types of surgery (oncological and non-oncological), including shorter durations of hospitalization, reduced postoperative pain and use of pain medication, and reduced blood loss and need for transfusions.[108–111]

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However, the evidence for improved immune and endocrine status following laparoscopy is less convincing. For example, whereas several randomized clinical trials (RCTs) indicated lower IL-6 levels following laparoscopy,[112,113] alterations in other key cytokines, including the immunosuppressive IL-10, are not clear,[114,115] neither are the effects on the number of circulating NK cells[112,116–118] and hormonal stress responses.[117,119] The lack of clear advantages for laparoscopic procedures according to these indices might be related to the more-complex nature of laparoscopic procedures, especially with regard to abdominal oncological surgeries. For example, laparo-scopy for colorectal cancer often necessitates more-extensive manipulations of internal organs and prolonged surgical duration; such surgery might have similar effects to an open abdominal surgery due to 'ceiling effects' in endocrine and immunological indices.[117]

More importantly, and not surprisingly given the above, oncological outcomes seem least affected by surgery type. Although a RCT in patients with colon cancer reported that laparoscopic surgery resulted in improved long-term cancer outcomes,[120] most RCTs have not shown significant differences in long-term outcomes, as reviewed in regard to colorectal,[121] endometrial[122] and ovarian[123] cancers.

Similarly, studies in our animal models, showed that adding laparotomy to a minor surgical procedure, or performing a more-traumatic surgery to excise a primary tumour[36] or administer syngeneic malignant cells,[124] resulted in worse immune outcomes, but did not significantly worsen cancer outcomes. Furthermore, in these studies, the use of a nonselective β-adrenergic antagonist and a COX2 inhibitor to attenuate the responses to surgery resulted in a similar degree of improvement in cancer outcomes (including overall survival rates) in minor and major surgical procedures.[36,125] These findings support the ceiling-effect hypothesis and the potential clinical benefits of perioperative interventions, such as COX2 inhibition and β-adrenergic blockade, both in minor and in major procedures.

On this basis, the priority of every surgeon should be to achieve complete excision of primary tumours (negative margins) and all evident or suspected metastatic foci, even at the expense of extending tissue damage and surgical trauma. Of note, the specific blockade of excess responses to surgery should be considered irrespective of the type of surgery.

Sex hormones and surgical responses in women

For decades, the phase of the menstrual cycle and the levels of sex hormones during surgery in premenopausal and in postmenopausal women have been subject of debate in terms of their impact on long-term cancer outcomes in women with breast cancer.[126–129] One hypothesis is that high oestrogen levels concurrently with low progesterone levels is a major risk factor for metastatic progression,[127] possibly because this hormonal pattern promotes a greater immunosuppression.[130] Indeed, a recent pivotal RCT in 1,000 women with breast cancer showed that a single preoperative administration of hydroxyprogesterone (a synthetic progesterone), which disrupts this hormonal pattern, substantially reduced recurrence rates in lymph-node-positive patients, but not in lymph-node-negative patients.[11]

The findings of this RCT indicate the causal impact of sex hormones on cancer outcomes in a context of surgical tumour excision, and thus also suggest that the relatively minor surgery

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for breast cancer excision can have profound effects on the metastatic process.[11] Specifically, we believe that the fact that a specific temporary hormonal status on the day of surgery has a considerable long-lasting impact indicates that either surgery dramatically potentiates an effect of sex hormones, or that sex hormones modulate the profound effects of surgery—highlighting the key influence of biological factors during the perioperative period in determining cancer outcome. Furthermore, we suggest that the underlying mechanism is a facilitation of a pre-existing metastatic process by surgery. This assertion is supported by several characteristics of the RCT and other studies indicating the perioperative effects of sex hormones on cancer outcomes, specifically, that they were observed in women with positive but not negative lymph nodes, were due to distal malignant recurrence, were not evident before 3 years post-surgery, and were independent of tumour hormone receptor status.[11,128] These observations suggest that surgery potentiated an ongoing metastatic process, not through direct effects of sex hormones on the malignant tissue (as it was independent of receptor status), but through an indirect mechanism, such as immunosuppression[131,132] or other processes that facilitate progression of an early stage of a metastatic process.[11,127]

To simulate this phenomenon, we used a rat model of mammary adenocarcinoma metastasis, and directly showed that the influence of hormonal/oestrous status occurs in the context of surgery or β-adrenoceptor stimulation, but not in their absence.[131,133] Similarly, *in vitro* the levels of β-adrenergic suppression of cytotoxic activity of NK cells harvested from both women and rats were dependent on the menstrual/oestrous phase during which blood was withdrawn.[131–133] These results directly indicate that the menstrual and oestrous cycles modulate the susceptibility of NK cells to suppression by adrenaline or noradrenaline, which might stem from the findings that sex hormones modulate the expression levels of adrenergic receptors on lymphocytes and NK cells.[134]

Overall, because it might not be clinically practical to restrict surgery for women with a specific sex hormone status,[135] and as most oncological patients are post-menopausal, one might consider progesterone administration and/or β-adrenergic blockade as prophylactic measures.[11]

Psychological stress

Patients with cancer are naturally subject to emotional distress,[136,137] from cancer diagnosis, through operation and adjuvant therapies (that also generate concerns about body deformation especially in patients with breast cancer), and continuing for years, owing to the ongoing struggles and fears of social isolation, disease recurrence, and death. Of note, psychological factors, such as stress and anxiety, trigger marked endocrinological and immunological responses, which during the perioperative and following periods could influence cancer progression and long-term survival rates, similarly to the effects of physiological factors. Indeed, stress responses that are not related to tissue damage were reported as risk factors for metastatic progression in numerous animal studies,[47,138] and also in some clinical trials.[139–141]

Specifically, patients who expressed high subjective stress levels when first diagnosed with cancer exhibited lower levels of NK-cell activity.[142,143] Moreover, the quality of emotional

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support received by the patients was the main predictor of NK-cell cytotoxicity once patients were discharged from hospital.[144] Not surprisingly, therefore, the management of cognitive-behavioural stress was efficient in decreasing systemic cortisol levels[145] and in reducing proinflammatory gene expression in circulating leukocytes.[146]

Nevertheless, psychological interventions in patients with cancer do not seem to reliably improve long-term oncological outcomes.[139–141,147–149] Inconsistent findings, and the overall scarcity of positive outcomes, despite decades of research, suggest a moderate or lack of improvement in long-term cancer outcomes by common psychological interventions.

We suggest that, although stress is predominant throughout the disease, its influence on survival occurs mainly during the short perioperative timeframe, which rarely includes psychological interventions. Indeed, psycho logical therapy provided solely throughout hospitalization has been shown to result in improved survival rates,[140] whereas postsurgical therapy did not.[148,149] Furthermore, because both psychological and physiological factors activate most neuroendocrine stress responses perioperatively, interventions to circumvent only the psychological stress could be insufficient, and would be less effective than pharmacological interventions, such as administration of β-blockers, that are expected to counteract stress responses of any origin—emotional or physiological.

We, therefore, encourage psychological interventions throughout the disease timeframe, especially perioperatively, if feasible. However, during the peri-operative period, psychological interventions cannot replace pharmacological interventions, and should be introduced carefully without burdening patients with responsibility for their own stress responses.

Nutritional status and nutritional support

Nutritional interventions have been repeatedly shown to affect immediate postsurgical outcomes;[150] however, their role in determining oncological outcomes remains unclear. On the one hand, reports from preclinical studies have raised concerns that excessive nutritional support, and specifically parenteral nutrition, could potentially lead to worse oncological outcomes by facilitating tumour-cell proliferation.[150] On the other hand, nutritional deficiencies, manifested as low pretreatment levels of serum albumin, have been repeatedly linked to worse oncological outcomes in gastrointestinal, lung, gynaecological, and other malignancies.[151]

Only one randomized trial has tested the effects of a nutritional intervention on oncological outcomes beyond the duration of the postsurgical hospitalization; in this study of 32 patients, perioperative arginine supplements markedly improved long-term survival of malnourished patients with head and neck cancer from a median of 20.7 months to 34.8 months.[152] A comprehensive multi-centre prospective cohort study assessing the relationship between nutrition, lifestyle factors, and colorectal-cancer recurrence is ongoing (the COLON study).[153]

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Potential perioperative interventions

β–adrenergic blockers and COX2 inhibitors

As indicated throughout this Review, a variety of peri-operative processes that are associated with increased risk for cancer recurrence are triggered through excess release of catecholamines and/or prostaglandins. Indeed, both animal studies and clinical retrospective studies suggest that their blockade can be an efficient therapeutic approach.

In animal models involving xenograft of human malignancies or syngeneic cancer cell lines, the use of the nonselective β-adrenergic blocker propranolol, and the selective COX2 inhibitor etodolac resulted in reduced endocrine[36] and angiogenic[154] perturbations, improved antimetastatic immunity,[35,36] attenuated surgery-induced potentiation of metastasis,[36,125,154] and improved long-term survival rates.[36] In some studies, only the combined use of the two drugs was effective,[35,36] which can be attributed to the abundance of both catecholamines and prostaglandins during the perioperative period, in conjuncture with redundancy in their impact on intracellular cascades in immunocytes (both activate the cAMP–PKA pathway) and redundancy in their impact on proangiogenic processes.[12]

In humans, the chronic use of COX inhibitors or of β-blockers in healthy peoples is an efficient chemopreventive measure against the formation of primary tumours of various origins,[155] including the breast and colon.[156,157] Moreover, regular users of nonselective β-blockers (for example, those treated for blood pressure), in whom epithelial ovarian, primary peritoneal, or fallopian-tube cancers have been diagnosed, exhibited a markedly prolonged survival period.[158]

The clinical use of such drugs only during the perioperative timeframe has been less frequently studied, but nevertheless yielded promising results. A low daily dose of the COX-inhibitor aspirin (25–50 mg per day) during the first postoperative year in patients with gastric and oesophageal cancer markedly improved 5-year survival rate, but only in patients with low-stage nondisseminated malignancies.[159] Three RCTs studied the short-term effects of COX2 inhibition (2–4 weeks before surgery) on tumour characteristics, in stage I–II primary breast cancer,[160] invasive transitional-cell carcinoma,[161] or prostate cancer.[162] The first two studies exhibited a modest increase in tumour-cell apoptosis,[160,161] whereas the third study also indicated a reduction in tumour-cell proliferation, microvessel density, angiogenesis and expression of the hypoxia inducible factor (HIF)-1α.[162] A retrospective study showed improved survival rates after intraoperative administration of a nonselective COX inhibitor, ketorolac, in patients undergoing surgery for breast or lung cancer (but not kidney cancer).[163] Furthermore, the use of β-blockers for several months before surgery, along with neoadjuvant therapy, in patients with triple-negative breast cancer, was associated with improved recurrence-free survival.[164] In patients with malignant nonmetastasized melanoma, the treatment with β-blockers was predictive of a reduced cancer-related and all-cause mortality, even when initiated ≤90 days before diagnosis and/or surgery,[165] but only in nonmetastasized disease. Together, these results suggest that treatment with β-blockers is indeed effective in controlling the initial stages of the metastatic process.

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As discussed above, regional anaesthesia that is added to general anaesthesia reduces sympathetic responses, and can thus be considered also as an anti-sympathetic intervention. Notably in the two studies that showed improved oncological outcomes when adding regional anaesthesia to general anaesthesia,[12,13] the therapeutic protocol for all patients included treatment with a COX inhibitor during surgery, further supporting the suggestion of synergistic effects of adrenergic blockade and COX inhibition.

Ultimately, we suggest that a combined use of an adrenergic blocker and a selective COX2 inhibitor, initiated a few days before surgery and continuing for a few weeks postoperatively (or longer), could result in a substantial decreases in cancer recurrence and in improved overall survival rates. The safety of this drug combination, in terms of tissue healing, has been shown in rats,[166] and we have now initiated two pilot RCTs testing the perioperative use of propranolol and etodolac in patients with colorectal and breast cancer (NCT00888797, NCT00502684).[167,168]

Statins and omega-3

Statins are a widely used group of lipid-lowering drugs; they inhibit the enzyme HMG-CoA, which has a major role in cholesterol formation in the liver. Omega-3 fatty acids are present in high concentration in several foods, including fish, and are used as a food supplement that can reduce blood levels of triglycerides.[169] Both statins and omega-3 fatty acids have been suggested as cancer chemopreventive agents, as well as anti-inflammatory treatments in the context of non-oncological and oncological surgeries,[170–172] which could potentially reduce postoperative growth of residual malignant cells.[173]

In a population-based study in Denmark that assessed mortality among 295,925 patients with cancer, reduced cancer-related mortality was observed in patients treated regularly with statins in 13 of 27 cancer types analysed,[174] particularly in prostate and colorectal cancers, but not in melanoma, as also shown by others.[175–177] In a pioneering RCT in patients with hepatocellular carcinoma, daily statin treatment for 16.5 months ± 9.8 months after transcatheter arterial chemoembolization resulted in a doubling in survival duration.[178] Furthermore, in rats injected with lymphoma cells, statin treatment markedly decreased the formation of metastases, but not the growth of the primary tumour.[179] Additionally, treatment of patients with high-grade breast cancer with statins for a few weeks preoperatively resulted in decreased levels of tumour proliferation markers and increased levels of apoptotic markers,[180] suggesting reduced metastatic growth.[181,182]

The use of omega-3 fatty acids was associated with clinically relevant attenuation of postoperative immuno-suppression and infection,[183–186] and increases the response rate to chemotherapy and 1-year survival among patients with advanced non-small-cell lung cancer.[187] Omega-3 fatty acids also increased resistance to experimental and spontaneous metastasis, and increased recurrence-free survival following excision of metastasizing primary tumours in animal models.[186,188]

Several biological mechanisms could underlie the beneficial oncological effects of omega-3 and statins.[189] First, both statins and omega-3 have well-established overall anti-inflammatory effects, that are translated into reduced systemic levels of C-reactive

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protein,[190,191] an *in vitro* shift towards type-2 T helper cell (T_H2) dominance,[192] and reduced lipopolysaccharide-induced IL-6 production.[193] Furthermore, long-chain omega-3 fatty acids are known to decrease the production of inflammatory cytokines, eicosanoids, and prostaglandins.[189] Second, at clinically relevant concentrations,[194] statins have been shown to arrest tumour-cell growth[195] and to induce apoptosis in the majority of tumour-derived cell lines tested *in vitro*, including neuroblastoma, juvenile monomyelocytic leukaemia, and some breast and prostate carcinomas.[196–198]

Interestingly, statins have a synergistic effect with COX inhibitors[199] that, *in vitro*, leads to G0–G1 phase cell-cycle arrest[200] and to enhanced apoptosis in several cell lines.[200,201] Furthermore, administration of these drugs *in vivo* following injection of malignant cells into rodents delayed tumour formation and reduced tumour volume.[201,202]

In conclusion, prolonged use of statins or omega-3 might reduce the prevalence of some types of cancer. Of note, the perioperative administration of these drugs is likely to exert beneficial effects by minimizing the metastatic process, effects that might synergize with the impact of NSAIDs, including COX2 inhibitors. Such safe and inexpensive approaches should be evaluated in clinical studies.

Perioperative immune stimulation

Early approaches to immune stimulation were based on cytokine delivery (IL-2, IL-12, or IFN-α), and although efficient in attenuating metastases in animal models[203] and in some clinical studies,[204] this method caused severe systemic adverse responses, including pyrogenic effects indistinguishable from signs of infections.[204] Therefore, such approaches are rarely considered for perioperative use, despite the acknowledged capacity of the immune system to attenuate the metastatic process.[2]

However, some synthetic agents that trigger endogenous immune responses have recently been approved by the FDA, and were shown to induce effective, self-limited, balanced, multi-cytokine responses with minimal adverse effects. One such agent is the Toll-like receptor (TLR)-9 agonist, class C CpG oligodeoxynucleotide (CpG), which activates NK cells, B cells, and plasmacytoid dendritic cells.[205] In mice, CpG was shown to have both cancer preventive and therapeutic effects,[206–208] and in rats, was demonstrated to diminish metastatic progression when injected one day before surgery.[209] In the clinic, CpG is being tested as an adjuvant to chemotherapeutic agents in several cancer types,[210,211] but has not been tested in the perioperative context. A more-recently introduced agent is the TLR4 agonist, glucopyranosyl lipid adjuvant (GLA), which activates T cells and dendritic cells. This compound is safe as an influenza vaccine adjuvant,[212] and ongoing studies testing the effect of this compound on cancer progression in the perioperative context in animal models are promising.[213]

Despite these encouraging data, several obstacles to effective and safe perioperative use of immune stimulation should be circumvented. Animal studies have shown that stress exposure alongside immune stimulation with IL-12 or CpG counteracted the beneficial effects of these agents on antimetastatic immune activity.[61,62] Such stress responses, which occur naturally in patients with cancer but not in animal models, might partly explain the

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discrepancy between the promising results of immune stimulation exhibited in animal models and the more-modest success of this approach in clinical trials. Moreover, even when effective immune stimulation is achieved, surgery and/or psychological stress can markedly suppress immunity, rendering immune stimulation ineffective in the peri-operative context.[214] To overcome these obstacles, we have combined preoperative immune stimulation (with CpG, IL-12, or polyinosine-polycytidylic acid) with β-blocker and/or a COX2 inhibitor in several animal models, and found that this integrative approach is markedly more effective than using each of these interventions alone.[43,203]

Importantly, some immune-stimulating agents can directly or indirectly potentiate tumour progression, as was shown with respect to granulocyte-macrophage colony-stimulating factor (GM-CSF).[215] Such adverse effects can be mediated by specific prometastatic cytokines, stress hormones known to be induced by immune stimulators, or by preoperative selection of resistant tumour cells as a result of too early and prolonged preoperative immune activation.

Enhanced recovery after surgery

The effects of numerous perioperative interventions on immediate postsurgical outcomes have been studied extensively over the years. The results from these studies have been analysed and integrated into Enhanced Recovery After Surgery (ERAS) guidelines in various surgical arenas.[216] ERAS is an evidence-based, comprehensive, multimodal approach designed to achieve early recovery for patients undergoing major surgery. Despite outstanding results in the immediate postsurgical settings, with up to a 50% reduction in postoperative complications, and a 30% reduction in care time,[217–219] no study has yet reported the oncological outcomes of these new approaches. As ERAS guidelines often overlap with the principles presented herein to limit the deleterious effects of surgeries on cancer recurrence (for example, minimizing the systemic use of opiates), it is our recommendation to evaluate each guideline based on the recommendations presented herein, and, if no contradictions found, to incorporate them in conjunction with studying oncological outcomes.

Conclusions

Ample evidence suggests that some biological perturbations during the critical perioperative period can markedly alter metastatic progression, and consequently affect long-term oncological outcomes. Having identified some surgical factors and their endocrine mediators, physicians can now use this knowledge to initiate much-needed clinical research to prevent such deleterious effects through short and safe perioperative interventions. Tables 1 and 2 summarize our recommendations on how one could implement such an approach in routine practice or clinical trials. Clearly, it is necessary to tailor potential interventions to specific cancer surgeries and patient characteristics. One should also strive to eliminate as many deleterious aspects of surgery as possible due to multiple converging responses to surgery. Of note, many of the discussed surgical aspects affect cancer progression by inducing unnecessarily profound stress and inflammatory responses. Accordingly, a combined nonselective β-adrenergic blockade and COX2 inhibition approach, which is safe

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and effective, could be used in the clinic during the perioperative timeframe. Importantly, the malignant tissue continuously mutates,[220] and with time and increasing selective pressure develops more-effective escape mechanisms. Thus, it would theoretically be favourable to initiate new antimetastatic interventions as late as possible before surgery, rather than as early as possible, to refrain from inducing a more-resistant tumour and micrometastases before surgery. Such interventions should be continued for at least few days or even weeks postoperatively to overlap and counteract physiological perturbations induced by surgery. On the basis of the limited relevant clinical literature, it seems that the proposed interventions would be more effective in patients without overt pre-existing metastases, but this suggestion should be tested. Finally, it should be noted that the perioperative period is generally underused therapeutically, as most standard neoadjuvant or adjuvant therapies are contraindicated immediately before or after surgery. Our therapeutic recommendations use this critical gap in treatment as a window of opportunity for safe and inexpensive interventions that might substantially affect cancer progression, potentially increasing survival rates in patients with cancer.

References

1. Neeman E, Zmora O, Ben-Eliyahu S. A new approach to reducing postsurgical cancer recurrence: perioperative targeting of catecholamines and prostaglandins. Clin Cancer Res. 2012; 18:4895–4902. [PubMed: 22753587]
2. Neeman E, Ben-Eliyahu S. Surgery and stress promote cancer metastasis: new outlooks on perioperative mediating mechanisms and immune involvement. Brain Behav Immun. 2013; 30(Suppl):S32–S40. [PubMed: 22504092]
3. Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth. 2010; 105:106–115. [PubMed: 20627881]
4. Yamaguchi K, Takagi Y, Aoki S, Futamura M, Saji S. Significant detection of circulating cancer cells in the blood by reverse transcriptase-polymerase chain reaction during colorectal cancer resection. Ann Surg. 2000; 232:58–65. [PubMed: 10862196]
5. Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E. Presence of a growth-stimulating factor in serum following primary tumor removal in mice. Cancer Res. 1989; 49:1996–2001. [PubMed: 2702641]
6. O'Reilly MS, et al. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. Cell. 1997; 88:277–285. [PubMed: 9008168]
7. Abramovitch R, Marikovsky M, Meir G, Neeman M. Stimulation of tumour growth by wound-derived growth factors. Br J Cancer. 1999; 79:1392–1398. [PubMed: 10188881]
8. Armaiz-Pena GN, Cole SW, Lutgendorf SK, Sood AK. Neuroendocrine influences on cancer progression. Brain Behav Immun. 2013; 30(Suppl):S19–S25. [PubMed: 22728325]
9. Gullino PM. Prostaglandins and gangliosides of tumor microenvironment: their role in angiogenesis. Acta Oncol. 1995; 34:439–441. [PubMed: 7540024]
10. Kim R, Emi M, Tanabe K, Arihiro K. Tumor-driven evolution of immunosuppressive networks during malignant progression. Cancer Res. 2006; 66:5527–5536. [PubMed: 16740684]
11. Badwe R, et al. Single-injection depot progesterone before surgery and survival in women with operable breast cancer: a randomized controlled trial. J Clin Oncol. 2011; 29:2845–2851. [PubMed: 21670457]
12. Biki B, et al. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiology. 2008; 109:180–187. [PubMed: 18648226]
13. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology. 2006; 105:660–664. [PubMed: 17006061]
14. Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000; 85:109–117. [PubMed: 10927999]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

15. Shakhar G, Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: could they reduce recurrence rates in oncological patients? Ann Surg Oncol. 2003; 10:972–992. [PubMed: 14527919]
16. Buvanendran A, et al. Upregulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. Anesthesiology. 2006; 104:403–410. [PubMed: 16508385]
17. Traynor C, Hall GM. Endocrine and metabolic changes during surgery: anaesthetic implications. Br J Anaesth. 1981; 53:153–160. [PubMed: 7008816]
18. Bartal I, et al. Immune perturbations in patients along the perioperative period: alterations in cell surface markers and leukocyte subtypes before and after surgery. Brain Behav Immun. 2010; 24:376–386. [PubMed: 19254757]
19. Rosenne E, et al. In vivo suppression of NK cell cytotoxicity by stress and surgery: glucocorticoids have a minor role compared to catecholamines and prostaglandins. Brain Behav Immun. 2014; 37:207–219. [PubMed: 24333572]
20. Perez-Sayans M, et al. β-adrenergic receptors in cancer: therapeutic implications. Oncol Res. 2010; 19:45–54. [PubMed: 21141740]
21. Wu WK, Sung JJ, Lee CW, Yu J, Cho CH. Cyclooxygenase-2 in tumorigenesis of gastrointestinal cancers: an update on the molecular mechanisms. Cancer Lett. 2010; 295:7–16. [PubMed: 20381235]
22. Mathew B, et al. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. Anesth Analg. 2011; 112:558–567. [PubMed: 21156980]
23. Bernabe DG, Tamae AC, Biasoli ER, Oliveira SH. Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells. Brain Behav Immun. 2011; 25:574–583. [PubMed: 21187140]
24. van der Bij GJ, et al. The perioperative period is an underutilized window of therapeutic opportunity in patients with colorectal cancer. Ann Surg. 2009; 249:727–734. [PubMed: 19387333]
25. Masur K, Niggemann B, Zanker KS, Entschladen F. Norepinephrine-induced migration of SW 480 colon carcinoma cells is inhibited by β-blockers. Cancer Res. 2001; 61:2866–2869. [PubMed: 11306460]
26. Kerros C, Brood I, Sola B, Jauzac P, Allouche S. Reduction of cell proliferation and potentiation of Fas-induced apoptosis by the selective kappa-opioid receptor agonist U50 488 in the multiple myeloma LP-1 cells. J Neuroimmunol. 2010; 220:69–78. [PubMed: 20163878]
27. Roche-Nagle G, Connolly EM, Eng M, Bouchier-Hayes DJ, Harmey JH. Antimetastatic activity of a cyclooxygenase-2 inhibitor. Br J Cancer. 2004; 91:359–365. [PubMed: 15213717]
28. Sood AK, et al. Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis. J Clin Invest. 2010; 120:1515–1523. [PubMed: 20389021]
29. Thaker PH, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med. 2006; 12:939–944. [PubMed: 16862152]
30. Wei D, et al. Celecoxib inhibits vascular endothelial growth factor expression in and reduces angiogenesis and metastasis of human pancreatic cancer via suppression of Sp1 transcription factor activity. Cancer Res. 2004; 64:2030–2038. [PubMed: 15026340]
31. Yang EV, et al. Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. Brain Behav Immun. 2009; 23:267–275. [PubMed: 18996182]
32. Inbar S, et al. Do stress responses promote leukemia progression? An animal study suggesting a role for epinephrine and prostaglandin-E_2 through reduced NK activity. PLoS ONE. 2011; 6:e19246. [PubMed: 21559428]
33. Kalinski P. Regulation of immune responses by prostaglandin E_2. J Immunol. 2012; 188:21–28. [PubMed: 22187483]
34. Yakar I, et al. Prostaglandin E_2 suppresses NK activity *in vivo* and promotes postoperative tumor metastasis in rats. Ann Surg Oncol. 2003; 10:469–479. [PubMed: 12734098]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

35. Benish M, et al. Perioperative use of β-blockers and COX-2 inhibitors may improve immune competence and reduce the risk of tumor metastasis. Ann Surg Oncol. 2008; 15:2042–2052. [PubMed: 18398660]
36. Glasner A, et al. Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a β-adrenergic antagonist and a cyclooxygenase-2 inhibitor. J Immunol. 2010; 184:2449–2457. [PubMed: 20124103]
37. Greenfeld K, et al. Immune suppression while awaiting surgery and following it: dissociations between plasma cytokine levels, their induced production, and NK cell cytotoxicity. Brain Behav Immun. 2007; 21:503–513. [PubMed: 17293081]
38. Smyth MJ, et al. Activation of NK cell cytotoxicity. Mol Immunol. 2005; 42:501–510. [PubMed: 15607806]
39. Shankaran V, et al. IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature. 2001; 410:1107–1111. [PubMed: 11323675]
40. Hodgson DM, Knott B. Potentiation of tumor metastasis in adulthood by neonatal endotoxin exposure: sex differences. Psychoneuroendocrinology. 2002; 27:791–804. [PubMed: 12183215]
41. Dewan MZ, et al. Role of natural killer cells in hormone-independent rapid tumor formation and spontaneous metastasis of breast cancer cells *in vivo*. Breast Cancer Res Treat. 2007; 104:267–275. [PubMed: 17066321]
42. Ben-Eliyahu S, Page GG, Yirmiya R, Taylor AN. Acute alcohol intoxication suppresses natural killer cell activity and promotes tumor metastasis. Nat Med. 1996; 2:457–460. [PubMed: 8597957]
43. Goldfarb Y, et al. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. Ann Surg. 2011; 253:798–810. [PubMed: 21475023]
44. Shakhar G, Ben-Eliyahu S. *In vivo* β-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats. J Immunol. 1998; 160:3251–3258. [PubMed: 9531281]
45. Landmann R. β-adrenergic receptors in human leukocyte subpopulations. Eur J Clin Invest. 1992; 22(Suppl. 1):30–36. [PubMed: 1333965]
46. Uotila P. The role of cyclic AMP and oxygen intermediates in the inhibition of cellular immunity in cancer. Cancer Immunol Immunother. 1996; 43:1–9. [PubMed: 8917629]
47. Ben-Eliyahu S, Shakhar G, Page GG, Stefanski V, Shakhar K. Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and β-adrenoceptors. Neuroimmunomodulation. 2000; 8:154–164. [PubMed: 11124582]
48. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011; 331:1565–1570. [PubMed: 21436444]
49. McCoy JL, Rucker R, Petros JA. Cell-mediated immunity to tumor-associated antigens is a better predictor of survival in early stage breast cancer than stage, grade or lymph node status. Breast Cancer Res Treat. 2000; 60:227–234. [PubMed: 10930110]
50. Detry O, Honore P, Meurisse M, Jacquet N. Cancer in transplant recipients. Transplant Proc. 2000; 32:127. [PubMed: 10700994]
51. Decaens T, et al. Role of immunosuppression and tumor differentiation in predicting recurrence after liver transplantation for hepatocellular carcinoma: a multicenter study of 412 patients. World J Gastroenterol. 2006; 12:7319–7325. [PubMed: 17143948]
52. Kantoff PW, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010; 363:411–422. [PubMed: 20818862]
53. Postow M, Callahan MK, Wolchok JD. Beyond cancer vaccines: a reason for future optimism with immunomodulatory therapy. Cancer J. 2011; 17:372–378. [PubMed: 21952288]
54. Kim JW, Eder JP. Prospects for Targeting PD-1 and PD-L1 in Various Tumor Types. Oncology. 2014; 28(Suppl. 3):pii, 202332.
55. Hegde S, Fox L, Wang X, Gumperz JE. Autoreactive natural killer T cells: promoting immune protection and immune tolerance through varied interactions with myeloid antigen-presenting cells. Immunology. 2010; 130:471–483. [PubMed: 20465577]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

56. Melamed R, et al. Marginating pulmonary-NK activity and resistance to experimental tumor metastasis: suppression by surgery and the prophylactic use of a β-adrenergic antagonist and a prostaglandin synthesis inhibitor. Brain Behav Immun. 2005; 19:114–126. [PubMed: 15664784]
57. Melamed R, et al. The marginating-pulmonary immune compartment in rats: characteristics of continuous inflammation and activated NK cells. J Immunother. 2010; 33:16–29. [PubMed: 19952959]
58. Luo DZ, et al. On the cell biology of pit cells, the liver-specific NK cells. World J Gastroenterol. 2000; 6:1–11. [PubMed: 11819514]
59. Macleod AS, Havran WL. Functions of skin-resident γδ T cells. Cell Mol Life Sci. 2011; 68:2399–2408. [PubMed: 21560071]
60. Larmonier N, Fraszczak J, Lakomy D, Bonnotte B, Katsanis E. Killer dendritic cells and their potential for cancer immunotherapy. Cancer Immunol Immunother. 2010; 59:1–11. [PubMed: 19618185]
61. Goldfarb Y, Levi B, Sorski L, Frenkel D, Ben-Eliyahu S. CpG-C immunotherapeutic efficacy is jeopardized by ongoing exposure to stress: potential implications for clinical use. Brain Behav Immun. 2011; 25:67–76. [PubMed: 20656015]
62. Levi B, et al. Continuous stress disrupts immunostimulatory effects of IL-12. Brain Behav Immun. 2011; 25:727–735. [PubMed: 21277367]
63. Prigione I, et al. Reciprocal interactions between human mesenchymal stem cells and γδ T cells or invariant natural killer T cells. Stem Cells. 2009; 27:693–702. [PubMed: 19096038]
64. Martinet L, Poupot R, Fournie JJ. Pitfalls on the roadmap to γδ T cell-based cancer immunotherapies. Immunol Lett. 2009; 124:1–8. [PubMed: 19465238]
65. Bodey B, Bodey B Jr, Siegel SE, Kaiser HE. Failure of cancer vaccines: the significant limitations of this approach to immunotherapy. Anticancer Res. 1999; 20:2665–2676.
66. Azrad M, Demark-Wahnefried W. The association between adiposity and breast cancer recurrence and survival: a review of the recent literature. Curr Nutr Rep. 2014; 3:9–15. [PubMed: 24533234]
67. Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. Breast. 2013; 22(Suppl. 2):S30–S37. [PubMed: 24074789]
68. Heaney A, Buggy DJ. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis? Br J Anaesth. 2012; 109(Suppl. 1):i17–i28. [PubMed: 23242747]
69. Schlagenhauff B, et al. Prognostic impact of the type of anaesthesia used during the excision of primary cutaneous melanoma. Melanoma Res. 2000; 10:165–169. [PubMed: 10803717]
70. Myles PS, et al. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. BMJ. 2011; 342:d1491. [PubMed: 21447587]
71. Gottschalk A, et al. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. Anesthesiology. 2010; 113:27–34. [PubMed: 20508494]
72. Tsui BC, et al. Epidural anesthesia and cancer recurrence rates after radical prostatectomy. Can J Anaesth. 2010; 57:107–112. [PubMed: 19911247]
73. US National Library of Medicine. ClinicalTrials.gov. 2012. [online], https://clinicaltrials.gov/ct2/show/NCT00684229?term=NCT00684229&rank=1
74. US National Library of Medicine. ClinicalTrials.gov. 2013. [online], https://clinicaltrials.gov/ct2/show/NCT00418457?term=NCT00418457&rank=1
75. US National Library of Medicine. ClinicalTrials.gov. 2011. [online], https://clinicaltrials.gov/ct2/show/NCT01179308?term=NCT01179308&rank=1
76. Deegan CA, et al. Effect of anaesthetic technique on oestrogen receptor-negative breast cancer cell function *in vitro*. Br J Anaesth. 2009; 103:685–690. [PubMed: 19776028]
77. Page GG, Ben Eliyahu S, Yirmiya R, Liebeskind JC. Morphine attenuates surgery-induced enhancement of metastatic colonization in rats. Pain. 1993; 54:21–28. [PubMed: 8378099]
78. Shavit Y, Ben-Eliyahu S, Zeidel A, Beilin B. Effects of fentanyl on natural killer cell activity and on resistance to tumor metastasis in rats. Dose and timing study Neuroimmunomodulation. 2004; 11:255–260. [PubMed: 15249732]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

79. Afsharimani, B., Doornebal, CW., Cabot, PJ., Hollmann, MW., Parat, MO. Comparison and analysis of the animal models used to study the effect of morphine on tumour growth and metastasis. Br J Pharmacol. 2014. http://dx.doi.org/10.1111/bph.12589
80. Bayer BM, Daussin S, Hernandez M, Irvin L. Morphine inhibition of lymphocyte activity is mediated by an opioid dependent mechanism. Neuropharmacology. 1990; 29:369–374. [PubMed: 2160624]
81. Yeager MP, et al. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology. 1995; 83:500–508. [PubMed: 7661350]
82. Page GG, Ben-Eliyahu S, Yirmiya R, Liebeskind JC. Morphine attenuates surgery-induced enhancement of metastatic colonization in rats. Pain. 1993; 54:21–28. [PubMed: 8378099]
83. Gaspani L, Bianchi M, Limiroli E, Panerai AE, Sacerdote P. The analgesic drug tramadol prevents the effect of surgery on natural killer cell activity and metastatic colonization in rats. J Neuroimmunol. 2002; 129:18–24. [PubMed: 12161016]
84. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. Anesth Analg. 2003; 97:1331–1339. [PubMed: 14570648]
85. Ben-Eliyahu S, Shakhar G, Rosenne E, Levinson Y, Beilin B. Hypothermia in barbiturate-anesthetized rats suppresses natural killer cell activity and compromises resistance to tumor metastasis: a role for adrenergic mechanisms. Anesthesiology. 1999; 91:732–740. [PubMed: 10485785]
86. Gupta A, Bjornsson A, Fredriksson M, Hallbook O, Eintrei C. Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in central Sweden. Br J Anaesth. 2011; 107:164–170. [PubMed: 21586443]
87. Lin L, et al. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. Br J Anaesth. 2011; 106:814–822. [PubMed: 21436156]
88. Cata JP, Gottumukkala V, Sessler DI. How regional analgesia might reduce postoperative cancer recurrence. Eur J Pain Suppl. 2011; 5:345–355.
89. Kao KJ. Mechanisms and new approaches for the allogeneic blood transfusion-induced immunomodulatory effects. Transfus Med Rev. 2000; 14:12–22. [PubMed: 10669937]
90. Lenhard V, Maassen G, Opelz G. Transfusion-induced enhancement of prostaglandin and thromboxane release in prospective kidney graft recipients. Proc Eur Dial Transplant Assoc Eur Ren Assoc. 1985; 21:923–927. [PubMed: 3887386]
91. Jensen LS, et al. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. Br J Surg. 1992; 79:513–516. [PubMed: 1611441]
92. Blumberg N, Heal JM. Effects of transfusion on immune function. Cancer recurrence and infection. Arch Pathol Lab Med. 1994; 118:371–379. [PubMed: 8166587]
93. Schriemer PA, Longnecker DE, Mintz PD. The possible immunosuppressive effects of perioperative blood transfusion in cancer patients. Anesthesiology. 1988; 68:422–428. [PubMed: 3278652]
94. Landers DF, Hill GE, Wong KC, Fox IJ. Blood transfusion-induced immunomodulation. Anesth Analg. 1996; 82:187–204. [PubMed: 8712400]
95. Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. Ann Surg. 2012; 256:235–244. [PubMed: 22791100]
96. Amato, A., Pescatori, M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database of Systematic Reviews. Art. No.: CD005033. http://dx.doi.org/10.1002/14651858.CD005033.pub2
97. Rosenberg SA, Seipp CA, White DE, Wesley R. Perioperative blood transfusions are associated with increased rates of recurrence and decreased survival in patients with high-grade soft-tissue sarcomas of the extremities. J Clin Oncol. 1985; 3:698–709. [PubMed: 3998786]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

98. Johnson JT, Taylor FH, Thearle PB. Blood transfusion and outcome in stage III head and neck carcinoma. Arch Otolaryngol Head Neck Surg. 1987; 113:307–310. [PubMed: 3814377]

99. Atzil S, et al. Blood transfusion promotes cancer progression: a critical role for aged erythrocytes. Anesthesiology. 2008; 109:989–997. [PubMed: 19034095]

100. Gohel MS, Bulbulia RA, Slim FJ, Poskitt KR, Whyman MR. How to approach major surgery where patients refuse blood transfusion (including Jehovah's Witnesses). Ann R Coll Surg Engl. 2005; 87:3–14. [PubMed: 15720900]

101. Martyn V, et al. The theory and practice of bloodless surgery. Transfus Apher Sci. 2002; 27:29–43. [PubMed: 12201468]

102. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Engl J Med. 1996; 334:1209–1215. [PubMed: 8606715]

103. Beilin B, et al. Effects of mild perioperative hypothermia on cellular immune responses. Anesthesiology. 1998; 89:1133–1140. [PubMed: 9822001]

104. Frank SM, et al. The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. A randomized clinical trial. Anesthesiology. 1995; 82:83–93. [PubMed: 7832339]

105. Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative hypothermia on blood loss and transfusion requirement. Anesthesiology. 2008; 108:71–77. [PubMed: 18156884]

106. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med. 1996; 334:1209–1215. [PubMed: 8606715]

107. Nduka CC, et al. Intraperitoneal hypothermia during surgery enhances postoperative tumor growth. Surg Endosc. 2002; 16:611–615. [PubMed: 11972199]

108. Walker JL, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol. 2009; 27:5331–5336. [PubMed: 19805679]

109. van der Pas MH, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol. 2013; 14:210–218. [PubMed: 23395398]

110. Breukink, S., Pierie, J., Wiggers, T. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database of Systematic Reviews. Art. No.: CD005200. http://dx.doi.org/10.1002/14651858.CD005200.pub3

111. Schwenk, W., Haase, O., Neudecker, J., Muller, JM. Short term benefits for laparoscopic colorectal resection. Cochrane Database of Systematic Reviews. Art. No.: CD003145. http://dx.doi.org/10.1002/14651858.CD003145.pub2

112. Wu FP, et al. Systemic and peritoneal inflammatory response after laparoscopic or conventional colon resection in cancer patients: a prospective, randomized trial. Dis Colon Rectum. 2003; 46:147–155. [PubMed: 12576886]

113. Sammour T, Kahokehr A, Chan S, Booth RJ, Hill AG. The humoral response after laparoscopic versus open colorectal surgery: a meta-analysis. J Surg Res. 2010; 164:28–37. [PubMed: 20828745]

114. Torres A, Torres K, Paszkowski T, Staskiewicz GJ, Maciejewski R. Cytokine response in the postoperative period after surgical treatment of benign adnexal masses: comparison between laparoscopy and laparotomy. Surg Endosc. 2007; 21:1841–1848. [PubMed: 17356933]

115. Sammour T, Kahokehr A, Zargar-Shoshtari K, Hill AG. A prospective case-control study of the local and systemic cytokine response after laparoscopic versus open colonic surgery. J Surg Res. 2012; 173:278–285. [PubMed: 21195431]

116. Wichmann MW, et al. Immunological effects of laparoscopic vs open colorectal surgery: a prospective clinical study. Arch Surg. 2005; 140:692–697. [PubMed: 16027336]

117. Landman J, et al. Prospective comparison of the immunological and stress response following laparoscopic and open surgery for localized renal cell carcinoma. J Urol. 2004; 171:1456–1460. [PubMed: 15017197]

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118. Hu JK, et al. Comparative evaluation of immune response after laparoscopical and open total mesorectal excisions with anal sphincter preservation in patients with rectal cancer. World J Gastroenterol. 2003; 9:2690–2694. [PubMed: 14669314]
119. Solomon MJ, Young CJ, Eyers AA, Roberts RA. Randomized clinical trial of laparoscopic versus open abdominal rectopexy for rectal prolapse. Br J Surg. 2002; 89:35–39. [PubMed: 11851660]
120. Lacy AM, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet. 2002; 359:2224–2229. [PubMed: 12103285]
121. Kuhry, E., Schwenk, WF., Gaupset, R., Romild, U., Bonjer, HJ. Long-term results of laparoscopic colorectal cancer resection. Cochrane Database of Systematic Review. Art. No.: CD003432. http://dx.doi.org/10.1002/14651858.CD003432.pub2
122. Galaal, K. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database of Systematic Review. Art. No.: CD006655. http://dx.doi.org/10.1002/14651858.CD006655.pub2
123. Lawrie, TA., et al. Laparoscopy versus laparotomy for FIGO stage I ovarian cancer. Cochrane Database of Systematic Review. Art. No.: CD005344. http://dx.doi.org/10.1002/14651858.CD005344.pub3
124. Sorski L, et al. The impact of surgical extent and sex on the hepatic metastasis of colon cancer. Surg Today. 2014; 44:1925–1934. [PubMed: 24190423]
125. Sorski L, et al. Do minimally-invasive surgical procedures reduce colorectal cancer progression? A severity-independent need for arresting surgically-induced stress responses using β-adrenergic blockers and COX2 inhibitors. Brain Behav Immun. 2011; 25:S200.
126. Hrushesky WJ, Bluming AZ, Gruber SA, Sothern RB. Menstrual influence on surgical cure of breast cancer. Lancet. 1989; 2:949–952. [PubMed: 2571865]
127. Badwe RA, et al. Timing of surgery during menstrual cycle and survival of premenopausal women with operable breast cancer. Lancet. 1991; 337:1261–1264. [PubMed: 1674070]
128. Lemon HM, Rodriguez-Sierra JF. Timing of breast cancer surgery during the luteal menstrual phase may improve prognosis. Nebr Med J. 1996; 81:73–78.
129. Samuel, M., Wai, KL., Brennan, VK., Yong, WS. Timing of breast surgery in premenopausal breast cancer patients. Cochrane Database of Systematic Review. Art. No.: CD003720. http://dx.doi.org/10.1002/14651858.CD003720.pub2
130. Ben-Eliyahu S, Page GG, Shakhar G, Taylor AN. Increased susceptibility to metastasis during pro-oestrus/oestrus in rats: possible role of oestradiol and natural killer cells. Br J Cancer. 1996; 74:1900–1907. [PubMed: 8980388]
131. Ben-Eliyahu S, Shakhar G, Shakhar K, Melamed R. Timing within the oestrous cycle modulates adrenergic suppression of NK activity and resistance to metastasis: possible clinical implications. Br J Cancer. 2000; 83:1747–1754. [PubMed: 11104576]
132. Shakhar K, Shakhar G, Rosenne E, Ben-Eliyahu S. Timing within the menstrual cycle, sex, and the use of oral contraceptives determine adrenergic suppression of NK cell activity. Br J Cancer. 2000; 83:1630–1636. [PubMed: 11104557]
133. Page GG, Ben-Eliyahu S. Increased surgery-induced metastasis and suppressed natural killer cell activity during proestrus/estrus in rats. Breast Cancer Res Treat. 1997; 45:159–167. [PubMed: 9342441]
134. Wheeldon NM, et al. Influence of sex-steroid hormones on the regulation of lymphocyte β_2-adrenoceptors during the menstrual cycle. Br J Clin Pharmacol. 1994; 37:583–588. [PubMed: 7917778]
135. Grant CS, et al. Menstrual cycle and surgical treatment of breast cancer: findings from the NCCTG N9431 study. J Clin Oncol. 2009; 27:3620–3626. [PubMed: 19487378]
136. Lutgendorf S, Costanzo E, Siegel S. Psychosocial influences in oncology: an expanded model of biobehavioral mechanisms. Psychoneuroimmunology. 2007; 4:869–896.
137. Garssen B, Boomsma MF, Beelen RH. Psychological factors in immunomodulation induced by cancer surgery: a review. Biol Psychol. 2010; 85:1–13. [PubMed: 20576501]
138. Stefanski V, Ben-Eliyahu S. Social confrontation and tumor metastasis in rats: defeat and β-adrenergic mechanisms. Physiol Behav. 1996; 60:277–282. [PubMed: 8804676]

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139. Fawzy FI, et al. Malignant melanoma Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. Arch Gen Psychiatry. 1993; 50:681–689. [PubMed: 8357293]
140. Kuchler T, Bestmann B, Rappat S, Henne-Bruns D, Wood-Dauphinee S. Impact of psychotherapeutic support for patients with gastrointestinal cancer undergoing surgery: 10-year survival results of a randomized trial. J Clin Oncol. 2007; 25:2702–2708. [PubMed: 17602075]
141. Andersen BL, et al. Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial. Cancer. 2008; 113:3450–3458. [PubMed: 19016270]
142. Andersen BL, et al. Stress and immune responses after surgical treatment for regional breast cancer. J Natl Cancer Inst. 1998; 90:30–36. [PubMed: 9428780]
143. Koga C, et al. Anxiety and pain suppress the natural killer cell activity in oral surgery outpatients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001; 91:654–658. [PubMed: 11402277]
144. Levy SM, et al. Perceived social support and tumor estrogen/progesterone receptor status as predictors of natural killer cell activity in breast cancer patients. Psychosom Med. 1990; 52:73–85. [PubMed: 2305024]
145. Phillips KM, et al. Stress management intervention reduces serum cortisol and increases relaxation during treatment for nonmetastatic breast cancer. Psychosom Med. 2008; 70:1044–1049. [PubMed: 18842742]
146. Antoni MH, et al. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. Biol Psychiatry. 2012; 71:366–372. [PubMed: 22088795]
147. Ross L, Boesen EH, Dalton SO, Johansen C. Mind and cancer: does psychosocial intervention improve survival and psychological well-being? Eur J Cancer. 2002; 38:1447–1457. [PubMed: 12110489]
148. Edelman S, Lemon J, Bell DR, Kidman AD. Effects of group CBT on the survival time of patients with metastatic breast cancer. Psychooncology. 1999; 8:474–481. [PubMed: 10607980]
149. Ross L, et al. No effect on survival of home psychosocial intervention in a randomized study of Danish colorectal cancer patients. Psychooncology. 2009; 18:875–885. [PubMed: 19137506]
150. Huhmann MB, August DA. Perioperative nutrition support in cancer patients. Nutr Clin Pract. 2012; 27:586–592. [PubMed: 22875752]
151. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010; 9:69. [PubMed: 21176210]
152. Buijs N, et al. Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. Am J Clin Nutr. 2010; 92:1151–1156. [PubMed: 20881073]
153. Winkels RM, et al. The COLON study: Colorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumour recurrence, survival and quality of life. BMC Cancer. 2014; 14:374. [PubMed: 24886284]
154. Lee JW, et al. Surgical stress promotes tumor growth in ovarian carcinoma. Clin Cancer Res. 2009; 15:2695–2702. [PubMed: 19351748]
155. Rothwell PM, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet. 2012; 379:1602–1612. [PubMed: 22440946]
156. Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: a population- based study. J Clin Oncol. 2011; 29:2635–2644. [PubMed: 21632503]
157. Powe DG, et al. β-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget. 2010; 1:628–638. [PubMed: 21317458]
158. Watkins J, et al. Improved outcomes with beta blocker use in epithelial ovarian cancer patients [abstract]. Gynecol Oncol. 2013; 130:e31.
159. Liu JF, Jamieson GG, Wu TC, Zhu GJ, Drew PA. A preliminary study on the postoperative survival of patients given aspirin after resection for squamous cell carcinoma of the esophagus or adenocarcinoma of the cardia. Ann Surg Oncol. 2009; 16:1397–1402. [PubMed: 19241108]
160. Martin LA, et al. Pre-surgical study of the biological effects of the selective cyclo-oxygenase-2 inhibitor celecoxib in patients with primary breast cancer. Breast Cancer Res Treat. 2010; 123:829–836. [PubMed: 20697803]

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161. Dhawan D, et al. Effects of short-term celecoxib treatment in patients with invasive transitional cell carcinoma of the urinary bladder. Mol Cancer Ther. 2010; 9:1371–1377. [PubMed: 20423998]
162. Sooriakumaran P, et al. A randomized controlled trial investigating the effects of celecoxib in patients with localized prostate cancer. Anticancer Res. 2009; 29:1483–1488. [PubMed: 19443354]
163. Forget P, et al. Neutrophil:lymphocyte ratio and intraoperative use of ketorolac or diclofenac are prognostic factors in different cohorts of patients undergoing breast, lung, and kidney cancer surgery. Ann Surg Oncol. 2013; 20(Suppl. 3):650–660.
164. Melhem-Bertrandt A, et al. β-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. J Clin Oncol. 2011; 29:2645–2652. [PubMed: 21632501]
165. Lemeshow S, et al. β-blockers and survival among Danish patients with malignant melanoma: a population-based cohort study. Cancer Epidemiol Biomarkers Prev. 2011; 20:2273–2279. [PubMed: 21933972]
166. Hazut O, et al. The effect of β-adrenergic blockade and COX-2 inhibition on healing of colon, muscle, and skin in rats undergoing colonic anastomosis. Int J Clin Pharmacol Ther. 2011; 49:545–554. [PubMed: 21888867]
167. US National Library of Medicine. ClinicalTrials.gov. 2011. [online], https://clinicaltrials.gov/ct2/show/NCT00888797?term=NCT00888797&rank=1
168. US National Library of Medicine. ClinicalTrials.gov. 2014. [online], https://clinicaltrials.gov/ct2/show/NCT00502684?term=NCT00502684&rank=1
169. Rader, DJ., Hobbs, HH. Harrisons Principles of Internal Medicine. 16th. Kasper, DL., editor. McGraw-Hill; 2005. p. 2286-2319.Ch 335
170. Narisawa T, et al. Chemoprevention by pravastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, of *N*-methyl-*N*-nitrosourea-induced colon carcinogenesis in F344 rats. Jpn J Cancer Res. 1996; 87:798–804. [PubMed: 8797885]
171. Berquin IM, Edwards IJ, Chen YQ. Multi-targeted therapy of cancer by omega-3 fatty acids. Cancer Lett. 2008; 269:363–377. [PubMed: 18479809]
172. Liakopoulos OJ, et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30,000 patients. Eur Heart J. 2008; 29:1548–1559. [PubMed: 18506053]
173. Graaf MR, Richel DJ, van Noorden CJ, Guchelaar HJ. Effects of statins and farnesyltransferase inhibitors on the development and progression of cancer. Cancer Treat Rev. 2004; 30:609–641. [PubMed: 15531395]
174. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med. 2012; 367:1792–1802. [PubMed: 23134381]
175. Poynter JN, et al. Statins and the risk of colorectal cancer. N Engl J Med. 2005; 352:2184–2192. [PubMed: 15917383]
176. Hamilton RJ, et al. Statin medication use and the risk of biochemical recurrence after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database. Cancer. 2010; 116:3389–3398. [PubMed: 20586112]
177. Dellavalle, RP., et al. Statins and fibrates for preventing melanoma. Cochrane Database of Systematic Review. Art. No.: CD003697. http://dx.doi.org/10.1002/14651858.CD003697.pub2
178. Kawata S, et al. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. Br J Cancer. 2001; 84:886–891. [PubMed: 11286466]
179. Matar P, et al. Inhibitory effect of lovastatin on spontaneous metastases derived from a rat lymphoma. Clin Exp Metastasis. 1999; 17:19–25. [PubMed: 10390143]
180. Garwood ER, et al. Fluvastatin reduces proliferation and increases apoptosis in women with high grade breast cancer. Breast Cancer Res Treat. 2010; 119:137–144. [PubMed: 19728082]
181. Pollack A, et al. Ki-67 staining is a strong predictor of distant metastasis and mortality for men with prostate cancer treated with radiotherapy plus androgen deprivation: Radiation Therapy Oncology Group Trial 92–02. J Clin Oncol. 2004; 22:2133–2140. [PubMed: 15169799]

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182. Zhao J, et al. TIP30/CC3 expression in breast carcinoma: relation to metastasis, clinicopathologic parameters, and p53 expression. Human Pathology. 2007; 38:293–298. [PubMed: 17097132]

183. Weiss G, et al. Immunomodulation by perioperative administration of n-3 fatty acids. Br J Nutr. 2002; 87(Suppl. 1):S89–S94. [PubMed: 11895158]

184. Ates E, et al. Perioperative immunonutrition ameliorates the postoperative immune depression in patients with gastrointestinal system cancer (prospective clinical study in 42 patients). Acta Gastroenterol Belg. 2004; 67:250–254. [PubMed: 15587331]

185. Berger MM, et al. Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial. Am J Clin Nutr. 2013; 97:246–254. [PubMed: 23269816]

186. Goldfarb Y, et al. Fish oil attenuates surgery-induced immunosuppression, limits postoperative metastatic dissemination and increases long-term recurrence-free survival in rodents inoculated with cancer cells. Clin Nutr. 2012; 31:396–404. [PubMed: 22122868]

187. Murphy RA, et al. Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. Cancer. 2011; 117:3774–3780. [PubMed: 21328326]

188. Hubbard NE, Lim D, Erickson KL. Alteration of murine mammary tumorigenesis by dietary enrichment with n-3 fatty acids in fish oil. Cancer Lett. 1998; 124:1–7. [PubMed: 9500184]

189. Calder PC. n-3 fatty acids, inflammation, and immunity—relevance to postsurgical and critically ill patients. Lipids. 2004; 39:1147–1161. [PubMed: 15736910]

190. Tziakas DN, et al. Effect of statins on collagen type I degradation in patients with coronary artery disease and atrial fibrillation. Am J Cardiol. 2008; 101:199–202. [PubMed: 18178406]

191. Dernellis J, Panaretou M. Effect of C-reactive protein reduction on paroxysmal atrial fibrillation. Am Heart J. 2005; 150:1064.

192. Hakamada-Taguchi R, et al. Inhibition of hydroxymethylglutaryl-coenzyme a reductase reduces T_H1 development and promotes T_H2 development. Circ Res. 2003; 93:948–956. [PubMed: 14563711]

193. Ikeda U, Shimada K. Statins and monocytes. Lancet. 1999; 353:2070.

194. Thibault A, et al. Phase I study of lovastatin, an inhibitor of the mevalonate pathway, in patients with cancer. Clin Cancer Res. 1996; 2:483–491. [PubMed: 9816194]

195. Jakobisiak M, Bruno S, Skierski JS, Darzynkiewicz Z. Cell cycle-specific effects of lovastatin. Proc Natl Acad Sci USA. 1991; 88:3628–3632. [PubMed: 1673788]

196. Dimitroulakos J, et al. Increased sensitivity of acute myeloid leukemias to lovastatin-induced apoptosis: a potential therapeutic approach. Blood. 1999; 93:1308–1318. [PubMed: 9949174]

197. Dimitroulakos J, Yeger H. HMG-CoA reductase mediates the biological effects of retinoic acid on human neuroblastoma cells: lovastatin specifically targets P-glycoprotein-expressing cells. Nat Med. 1996; 2:326–333. [PubMed: 8612233]

198. Dimitroulakos J, et al. Differential sensitivity of various pediatric cancers and squamous cell carcinomas to lovastatin-induced apoptosis: therapeutic implications. Clin Cancer Res. 2001; 7:158–167. [PubMed: 11205904]

199. Xiao H, Yang CS. Combination regimen with statins and NSAIDs: a promising strategy for cancer chemoprevention. Int J Cancer. 2008; 123:983–990. [PubMed: 18548583]

200. Xiao H, Zhang Q, Lin Y, Reddy BS, Yang CS. Combination of atorvastatin and celecoxib synergistically induces cell cycle arrest and apoptosis in colon cancer cells. Int J Cancer. 2008; 122:2115–2124. [PubMed: 18172863]

201. Zheng X, et al. Atorvastatin and celecoxib inhibit prostate PC-3 tumors in immunodeficient mice. Clin Cancer Res. 2007; 13:5480–5487. [PubMed: 17875778]

202. Reddy BS, et al. Prevention of azoxymethane-induced colon cancer by combination of low doses of atorvastatin, aspirin, and celecoxib in F 344 rats. Cancer Res. 2006; 66:4542–4546. [PubMed: 16618783]

203. Avraham R, et al. Synergism between immunostimulation and prevention of surgery-induced immune suppression: an approach to reduce post-operative tumor progression. Brain Behav Immun. 2010; 24:952–958. [PubMed: 20362661]

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204. Bohm M, et al. Pretreatment with interleukin-2 modulates perioperative immunodysfunction in patients with renal cell carcinoma. Folia Biol (Praha). 2003; 49:63–68. [PubMed: 12779014]
205. Krieg AM. Therapeutic potential of Toll-like receptor 9 activation. Nat Rev Drug Discov. 2006; 5:471–484. [PubMed: 16763660]
206. Novakovic S, Stegel V, Kopitar A, Ihan A, Novakovic BJ. Preventive and therapeutic antitumor effect of tumor vaccine composed of CpG ODN class C and irradiated tumor cells is triggered through the APCs and activation of CTLs. Vaccine. 2007; 25:8241–8256. [PubMed: 17980936]
207. Kunikata N, et al. Peritumoral CpG oligodeoxynucleotide treatment inhibits tumor growth and metastasis of B16F10 melanoma cells. J Invest Dermatol. 2004; 123:395–402. [PubMed: 15245441]
208. Kuramoto Y, Nishikawa M, Hyoudou K, Yamashita F, Hashida M. Inhibition of peritoneal dissemination of tumor cells by single dosing of phosphodiester CpG oligonucleotide/cationic liposome complex. J Control Release. 2006; 115:226–233. [PubMed: 16996162]
209. Goldfarb Y, et al. CpG-C oligodeoxynucleotides limit the deleterious effects of β-adrenoceptor stimulation on NK cytotoxicity and metastatic dissemination. J Immunother. 2009; 32:280–291. [PubMed: 19242372]
210. Lubaroff DM, et al. Phase I clinical trial of an adenovirus/prostate-specific antigen vaccine for prostate cancer: safety and immunologic results. Clin Cancer Res. 2009; 15:7375–7380. [PubMed: 19920098]
211. Smith DA, et al. Efficacy and safety of IMO-2055, a novel TLR9 agonist, in combination with erlotinib (E) and bevacizumab (bev) in patients (pts) with advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed following prior chemotherapy [abstract]. J Clin Oncol. 2012; 30(Suppl):e18047.
212. Behzad H, et al. GLA-SE, a synthetic Toll-like receptor 4 agonist, enhances T-cell responses to influenza vaccine in older adults. J Infect Dis. 2012; 205:466–473. [PubMed: 22147791]
213. Matzner P, et al. 87. The use of the newly developed synthetic TLR-4 agonistas an immuno-therapeutic agent in a cancer model. Brain Behav Immun. 2013; 32(Suppl):e25.
214. Schwartz Y, Avraham R, Benish M, Rosenne E, Ben-Eliyahu S. Prophylactic IL-12 treatment reduces postoperative metastasis: mediation by increased numbers but not cytotoxicity of NK cells. Breast Cancer Res Treat. 2008; 107:211–223. [PubMed: 17431763]
215. Faries MB, Hsueh EC, Ye X, Hoban M, Morton DL. Effect of granulocyte/macrophage colony-stimulating factor on vaccination with an allogeneic whole-cell melanoma vaccine. Clin Cancer Res. 2009; 15:7029–7035. [PubMed: 19903777]
216. Varadhan KK, Lobo DN, Ljungqvist O. Enhanced recovery after surgery: the future of improving surgical care. Crit Care Clin. 2010; 26:527–547. [PubMed: 20643305]
217. Gatt M, Khan S, MacFie J. In response to: Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr. 2010; 29:434–440. [PubMed: 20116145]
218. Lv L, Shao YF, Zhou YB. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2012; 27:1549–1554. [PubMed: 23001161]
219. Ren L, et al. Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial. World J Surg. 2012; 36:407–414. [PubMed: 22102090]
220. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002; 3:991–998. [PubMed: 12407406]

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Key points

- The perioperative timeframe—days before and after tumour excision—is pivotal in determining long-term cancer outcomes, disproportionally to its short duration
- Potential metastasis-promoting aspects of the perioperative period and of surgery include anxiety and stress, specific anaesthetics and analgesics, hypothermia, blood transfusion, tissue damage, specific sex hormones, nociception and pain
- Deleterious processes include excess and maladaptive perioperative responses at the paracrine, endocrine, and immune-system levels
- Potential novel interventions include specified modifications to surgical procedures, stress-reducing and anti-inflammatory approaches, such as perioperative administration of non-selective β-adrenergic blockers and COX2 inhibitors, and perioperative immune stimulation
- These interventions could transform the perioperative timeframe from being a prominent facilitator of metastatic progression, to a yet unexplored opportunity for arresting and/or eliminating residual disease

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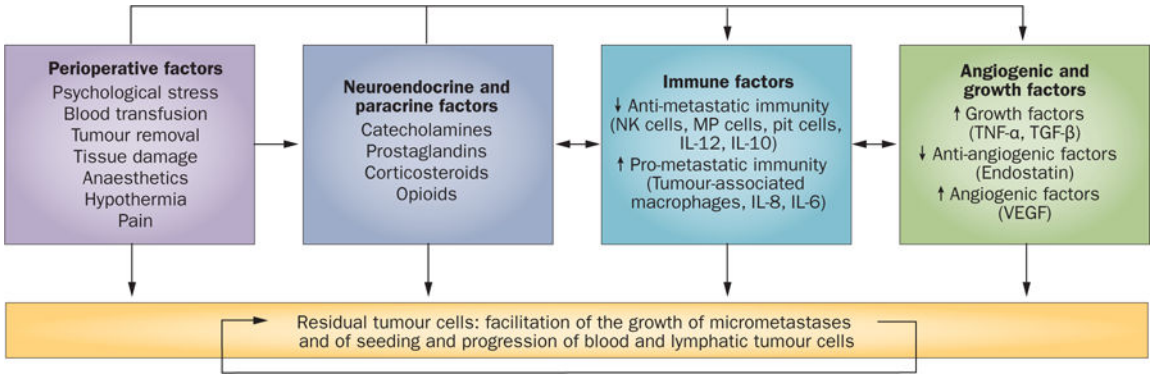

Figure 1.

A schematic presentation of major perioperative risk factors for tumour progression, and some of the neuroendocrine, paracrine, immunological, and angiogenic perturbations they elicit. These perturbations are mutually interactive and eventually affect malignant cells through directly interacting with them and/or through impacting their surrounding milieu.

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Table 1

Perioperative factors affecting long-term oncological outcomes

Surgical aspect	Suggested mediating mechanisms	Potential perioperative interventions	Evidence supporting intervention* (for references see text)
Anaesthesia and analgesia	Excess release of catecholamines, prostaglandins and glucocorticoids Direct effects on MRD Suppression of antimetastatic immunity: for example, NK-cell activity Pro-metastatic immune responses: for example T_{REG}-cell activity Increased angiogenesis and tumour proliferation	Replacing GA by RA or adding RA to GA Minimizing opiate use without compromising pain alleviation Substituting morphine/opiates with the pseudo-opiate tramadol Using β-adrenergic blockers and COX2 inhibitors	Animal: multiple consistent evidence Human: moderate evidence regarding cancer outcomes RCT: RA decreased VEGF levels (n = 22)
Blood transfusion	Excess release of prostaglandins Suppression of antimetastatic immunity: for example, NK-cell activity and immune tolerance Excess aberrant erythrocytes that apprehend immunocytes	Minimizing amount of blood transfused ('bloodless surgery') Use packed red cells and blood with short storage time Using COX2 inhibitors	Animal: few studies but with solid outcomes Human: good evidence regarding cancer outcomes RCT: advantage for packed cells over whole blood (n = 197); other aspects, such as age of transfused blood during surgery, were not studied
Intraoperative hypothermia	Excess release of catecholamines and glucocorticoids Suppression of antimetastatic immunity: for example, NK-cell activity, IL-1β, IL-2 and lymphocyte proliferation	Maintaining normothermia Using β-adrenergic blockers	Animal: multiple consistent evidence Human: none RCT: no effect in a single trial (n = 51)
Tissue damage extent: minimally invasive versus open surgery	Open surgery results in more profound suppression of antimetastatic immunity for some, but not other indices (for example, NK-cell number) Pro-metastatic immune responses: for example, IL-6 Proinflammatory responses	Using β-adrenergic blockers and COX2 inhibitors in both minimally invasive and open surgery	Animal: multiple studies showed only short-term benefits for minimally invasive surgery Human: only short-term benefits for laparoscopy RCT: inconsistent evidence regarding recurrence
Margins	Local residual disease	Achieving negative CRMs even if doing so necessitates extended tissue damage	Animal: multiple consistent evidence Human: good evidence regarding disease-free survival; inconsistent evidence regarding remote metastases RCT: none
Menstrual cycle: unopposed oestrogen (breast cancer)	Heightened expression levels of β-adrenergic receptors in cancer cells and lymphocytes Greater suppression of antimetastatic immunity: such as NK-cell activity Potentiated cancer-cell growth Facilitated shedding of tumour cells into the circulation	Administering hydroxyprogesterone to patients preoperatively, preferably to lymph-node-positive patients Operating during the hormonally validated luteal phase Using β-adrenergic blockers and COX2 inhibitors	Animal: few studies but with solid outcomes Human: inconsistent evidence regarding cancer outcomes, possibly due to inaccurate hormonal phase determination RCT: positive effect for hydroxyprogesterone injection (n = 1,000) in patients with lymph-node-positive breast cancer

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Surgical aspect	Suggested mediating mechanisms	Potential perioperative interventions	Evidence supporting intervention* (for references see text)
Psychological stress	Excess release of catecholamines, glucocorticoids, and other stress factors Suppression of antimetastatic immunity: for example, NK-cell activity and IL-12 production Elevated proinflammatory gene expression in circulating leukocytes	Using psychopharmacological or pharmacological stress-inhibiting interventions (for example, benzodiazepine or β-blockers) Initiating psychological intervention before surgery, as early as possible	Animal: multiple consistent evidence regarding immunity and cancer outcomes Human: influence on immune and endocrine factors RCT: inconsistent regarding cancer outcomes. Significant effects when interventions initiated before surgery

*Animal refers to studies in animal models of cancer; human refers to retrospective, and prospective non-randomized studies; and RCT refers to randomized clinical trials. Abbreviations: COX2, cyclooxygenase-2; CRM, circumferential resection margin; GA, general anaesthesia; MRD, minimal residual disease; NK, natural killer; T_{REG}, T regulatory; RA, regional anaesthesia; RCT, randomized clinical trial; VEGF, vascular endothelial growth factor.

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Table 2

Suggested perioperative therapeutic interventions

Intervention	Suggested mechanisms	Specifications	Major risks	Studies providing evidence of cancer outcomes*
Nonselective β-adrenergic blockers	Inhibits the impact of catecholamines on leukocytes, malignant cells, and their microenvironment	Synergizes with the benefits of COX2 inhibitors	Low blood pressure Asthma exacerbation Bradycardia	Animal: multiple consistent evidence, mostly using propranolol Human: good evidence in nonmetastasized disease RCT: none
Selective COX2 inhibitors	Reduces prostaglandin levels Anti-inflammatory Reduces glucocorticoid levels	Synergizes with the benefits of β-adrenergic blockers	Acute kidney injury Increased cardiovascular risk	Animal: multiple consistent evidence, mostly with etodolac Human: solid evidence in nonmetastasized disease RCT: none
Statins	Anti-inflammatory	NA	Myopathy/ rhabdomyolysis (rare) Increase in liver transaminase levels	Animal: few studies; some affecting primary tumours, others only metastases Human: chronic use correlate with decreased cancer rate and mortality in most cancer types RCT: improved tumour markers when given for few weeks (n = 40); improved survival when given for several months after TACE (n = 83)
Omega-3 fatty-acids	Anti-inflammatory	Reach high blood concentrations	NA	Animal: multiple consistent evidence Human: inconsistent evidence RCT: none
Immune stimulation	Stimulates anti-metastatic immunity	Induction of endogenous immune-response seems advantageous (for example, using TLR agonists) Perioperative stress might reduce efficacy	Pyrogenic effects, hypotension, dyspnoea, liver failure, renal failure, GI symptoms, anaemia, leukopenia, thrombocytopenia, exfoliative dermatitis, exacerbation of autoimmune diseases, neurological deficits, potentiation for tumour progression with some agents	Animal: few studies, solid outcomes Human: not yet tested perioperatively RCT: none
Psychological interventions	Inhibit stress responses	Should be effective when administered before surgery	NA	Animal: NA Human: influence on immune and endocrine factors RCT: inconsistent regarding cancer outcomes; significant

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Intervention	Suggested mechanisms	Specifications	Major risks	Studies providing evidence of cancer outcomes*
				effects when initiated before surgery
Hydroxyl-progesterone	Overcomes deleterious effects of unopposed oestrogen	Only tested in patients with breast cancer, but was independent of sex hormone receptor presentation	Miscarriage Hypercoagulability	Animal: a study with progesterone showed positive outcomes Human: none RCT: positive effect for hydroxyprogesterone injection in patients with lymph-node-positive breast cancer (n = 1,000)

*Animal refers to studies in animal models of cancer; human refers to retrospective, and prospective nonrandomized studies; and RCT refers to randomized clinical trials. Abbreviations: COX2, cyclooxygenase-2; GI, gastrointestinal; NA, not applicable; RCT, randomized clinical trial; TACE, transcatheter arterial chemoembolization; TLR, Toll-like receptors.