

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, disproportionately 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.

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Introduction

The perioperative period—days before to days–weeks following tumour excision—is short relative to the time-span of primary tumour evolution, 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 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 antiangiogenic 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.

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Competing interests

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Key points

- The perioperative timeframe—days before and after tumour excision—is pivotal in determining long-term cancer outcomes, disproportionately 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

However, if one can arrest these perioperative pro-metastatic 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 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 consequent 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 systemically 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 catecholamines²⁰ and prostaglandins,²¹ and their

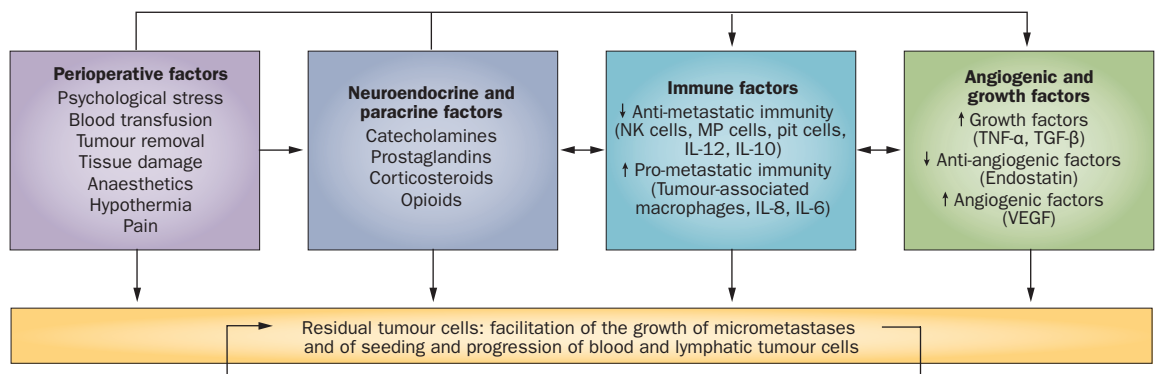


Figure 1 | A schematic presentation of major perioperative risk factors for tumour progression, and some of the neuroendocrine, paracrine, immunological, and angiogenic perturbations they elicit. These perturbations are mutually interactive and eventually affect malignant cells through directly interacting with them and/or through impacting their surrounding milieu.

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 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, macrophages, and dendritic cells.¹⁵ For example, NK cells are able to identify and kill malignant cells, inducing apoptosis through the perforin-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 intravenous 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 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.

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 perturbations⁸⁹ through increase in prostaglandin production⁹⁰ and other physiological alterations, which lead to suppression of NK activity⁹¹ 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 confounders (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 transfusion⁹² (also in a prospective study⁹¹), 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 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 undesirable effects of transfused erythrocytes were restricted to a short post-transfusion perioperative period, and can be explained by exhaustion of host antimetastatic immunocytes (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-1 β 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, nowadays, 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}

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, laparoscopy 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 endometrial¹²² and ovarian¹²³ 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 tumour³⁶ 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 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 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 levels¹⁴⁵ 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, psychological 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 perioperative 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 multicentre prospective cohort study assessing the relationship between nutrition, lifestyle factors, and colorectal-cancer recurrence is ongoing (the COLON study).¹⁵³

Potential perioperative interventions β -adrenergic blockers and COX2 inhibitors

As indicated throughout this Review, a variety of perioperative 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 endocrine³⁶ and angiogenic¹⁵⁴ 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)-1 α .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.

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 \pm 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 immunosuppression 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 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

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
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.

have been shown to arrest tumour-cell growth¹⁹⁵ 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 inhibitors¹⁹⁹ that, *in vitro*, leads to G0–G1 phase cell-cycle arrest²⁰⁰ 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 models²⁰³ 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

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 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.

(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 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 perioperative 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 pro-metastatic 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 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.

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Author contributions

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.