

# Are we causing the recurrence-impact of perioperative period on long-term cancer prognosis: Review of current evidence and practice

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## Abstract

Newer developments in the field of chemotherapeutic drug regimes, radiotherapy, and surgical techniques have improved the prognosis of cancer patients tremendously. Today increasing numbers of patients with aggressive disease are posted for surgical resection. The advances in reconstructive flap surgery offer the patient a near normal dignified postresection life. Hence, the expectations from the patients are also on the rise. Anesthetic challenges known in oncosurgery are that of difficult airway, maintenance of hemodynamics and temperature during long surgical hours, pain management, and postoperative intensive care management. But, recently acquired data raised the possibility of the anesthetic technique and conduct of perioperative period as a possible contributory factor in the growth and possible recurrence of the primary tumor. The foundation of the concept is somewhat fragile and not supported by conclusive evidence. In fact, like any other controversial topic in medicine, contradictory reports of the favorable effects of anesthetic technique and medications are plenty in the literature. This is the basis of our article where we have analyzed the current evidence available in the literature and how these and the forthcoming large scale studies may revolutionize the practice of oncoanesthesia.

**Key words:** Anesthesia, cancer recurrence, cytokines, hypothalamic-pituitary-adrenal axis, immunomodulation, interleukins, oncogenesis, stress response

## Introduction

The perioperative period is perhaps the most important time in the life of the residual cancer cells post-resection. Even with frozen section confirmed clear margins, 'minimal residual disease' remains due to intraoperative embolization of tumor cells into surrounding tissues.<sup>[1]</sup> Preexisting 'micrometastasis' also is a concern following resection of the primary tumor. Whether the extruded cancer cells left in the body will remount an attack depends on the tumor microenvironment during the perioperative period. Peach *et al.*, while analyzing the

prognostic significance of circulating tumor cells following surgical resection of primary tumor observed that presence of cancer cells in the circulation beyond 24 h is an independent predictor of increased tumor recurrence.<sup>[2]</sup> Theories based on available evidence suggest alterations in antigen presentation; secretion of immunosuppressive agents; and stimulation of inhibitory pathways by surgical stress, anesthetic medication, and other perioperative factors.<sup>[3]</sup> This can lead an otherwise occult nonthreatening residual minimal disease towards 'immune escape' and regrow to a full blown cancer. The impetus should be on controlling the immunosuppressive effects of perioperative physiology and maximizing host immunity for preventing cancer relapse.

## Historical evidence of interaction

Indirect observations pertaining to the complex interaction amongst perioperative events and immune system are not new. More than 30 years ago, cancer patients receiving ether anesthesia were reported to have a poorer outcome than those receiving halothane anesthesia,<sup>[4]</sup> indicating agent specificity on outcome. Evidences in support of the malleability of our immune system are plenty regarding blood transfusion and its favorable impact on graft survival in transplant patients<sup>[5]</sup> and

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the deleterious effect on tumor free survival in oncosurgery patients.<sup>[6]</sup>

### The immune system and cytokines

Following an immune challenge, host immune system is activated with the release of two types of self-regulatory protein hormones called “cytokines”.

1. The pro-inflammatory cytokines, e.g., tumor necrosis factor alpha (TNF $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), IL-6, and IL-8.
2. The anti-inflammatory cytokines, for example, IL-10, IL-1 receptor antagonist (IL-1 RA), and TNF binding proteins 1 and 2.

Upon exposure to the immune system the cancer cells undergoes a process of “immunoediting”<sup>[7]</sup> comprising of:

1. Elimination phase: Cells of the innate and adaptive immune system recognize and destroy tumor cells.
2. Equilibrium phase: Cancer cells are kept in check by the immune system.
3. Escape phase: Tumor cells escape immune destruction and manifest as overt tumors.

Our highly efficient immune system destroys almost all the residual cancer cells with <0.1% cells viable after 24 h of release.<sup>[8]</sup> Cell mediated immunity comprising of cytotoxic T lymphocytes (CTLs), the cluster of differentiation (CD) cells and natural killer (NK) cells forms the primary barrier against tumor immune-evasion.

### Perioperative events important for tumor recurrence

Perioperative immunosuppression starts early and lasts for days with a peak on day 3.<sup>[1]</sup> This can be the window for the tumor cells to mount an immune-evasion. The immunosuppression is characterized by loss of tumor surveillance, decrease in number of circulating NK cells, CTLs, and dendritic and T-helper cells.<sup>[9]</sup> Perioperative immunosuppression and hypermetabolic state can also magnify the adversity of neoadjuvant chemoradiotherapy and associated malnutrition.

Intraoperative manipulation and breach of tumor margin can release cancer cells into the systemic circulation. With the excision of primary tumor, mainly two things happen at the vascular level which can cause burst of angiogenesis and growth of micrometastasis:

- a. The source of protective antiangiogenic factors (angiostatin and endostatin) is eliminated.
- b. Release of vascular endothelial growth factor (VEGF) 1 and 2 and transforming growth factor b, which acts on its receptors expressed on vast majority of human solid tumors.<sup>[10-14]</sup> These coupled with anxiety, pain, blood

transfusion, hypothermia, hypoxia, organ hypoperfusion, hyperglycemia, and direct immunosuppressive effects of anesthetic agents creates an ideal environment for tumor growth.

### Psychological stress

The deleterious effect of stress on the immune system is evident from reports of stress induced deterioration of viral infection in humans.<sup>[15]</sup> Perioperative stress and anxiety stimulates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system leading to reduced NK cell activity and T-cell responses.<sup>[16]</sup> Episodes of depression which is common in cancer patients may adversely affect tumor prognosis and long-term survival.<sup>[17]</sup> To avoid the deleterious effect on the immune system, an aggressive approach to anxiolysis by counseling or pharmacological approach is important.

### Effect of surgery *per se*

Surgery induced stress can modify the neural, endocrine, metabolic, inflammatory, and immunologic microenvironment of the cell.<sup>[18]</sup> The magnitude of this immunosuppression is proportional to the degree of surgical manipulation.<sup>[19,20]</sup> Following a major surgery cellular immunity remains suppressed for several days with decrease in immunostimulating cytokines (IL-2, IL-12, and interferon (IFN)- $\gamma$ ) and increase in production of anti-inflammatory cytokines. Circulating levels of NK cells, dendritic cells, CTLs, and T-helper cells also decrease. The potential for minimally invasive surgery including robotic surgery to attenuate systemic inflammatory response is well-recognized<sup>[21]</sup> and can be the future technique of choice in oncosurgery.

### Effect of anesthesia

#### Intravenous anesthetic agents

Melamed *et al.*, reported a 5.5- and 2.0-fold increase in the number of viable tumor cells in the lungs at autopsy following ketamine and thiopental anesthesia, respectively.<sup>[22]</sup> This figure was not increased following propofol and diazepam, suggesting agent specificity on outcome.

#### Barbiturates

Short and intermediate acting barbiturates in clinically used concentrations have been shown to inhibit bactericidal functions of leukocytes as well as polarization, chemotaxis, adherence, phagocytosis and respiratory burst of neutrophils and monocytes.<sup>[23]</sup> The nuclear factor kappa B (NF- $\kappa$ B) has dual effects on the body. It inhibits cellular apoptosis and promotes tumor cell growth and at the same time improves immune and inflammatory response. Thiopentone inhibits the activation of (NF- $\kappa$ B) pathway.<sup>[24]</sup> In a small number of studies the inhibitory aspects of thiopental on nitric oxide (NO), an

important biological mediator of the inflammatory response has been investigated<sup>[25]</sup> and reports of strong association has been confirmed.

### Propofol

Propofol impairs monocyte and neutrophil functions similar to barbiturates<sup>[26]</sup> probably due to its lipid carrier vehicle. However, propofol is considered a 'safer drug' in oncoanesthesia owing to its predominant antitumor effects via inhibition of Cyclooxygenase (COX)-2 and Prostaglandin (PG) E2.<sup>[27]</sup> COX and PG E2 promote survival, invasiveness, angiogenesis and evasion of host immune surveillance by tumor cells.<sup>[26]</sup> Also, propofol has a weak  $\beta$ -adrenergic antagonist action<sup>[28]</sup> and can mitigate the stress induced immunomodulation better than isoflurane.<sup>[29]</sup>

### Other agents

Even as low a dose as 0.08 mg/kg of midazolam can inhibit lipopolysaccharide-induced production of IL-1 $\beta$ , TNF $\alpha$ , and IL-6 and 8 by monocytes.<sup>[30]</sup> Ketamine attenuates production of the pro-inflammatory cytokines, IL-6, and TNF $\alpha$  and suppresses NK cell function by peripheral  $\beta$ -adrenergic stimulation.<sup>[23]</sup>

### Volatile agents and nitrous oxide

Isoflurane and halothane can attenuate NK cell cytotoxicity induced by IFN therapy.<sup>[31]</sup> *In vitro* studies have pointed towards sevoflurane's ability to alter the release of cytokines (IL-1 $\beta$  and TNF $\alpha$ , but not IL-2).<sup>[32]</sup> Moreover, dose dependent genotoxicity by deoxyribonucleic acid (DNA) damage following exposure to inhalational anesthetic agents and nitrous oxide (N<sub>2</sub>O) can itself be a cause of oncogenesis. N<sub>2</sub>O in addition, depresses neutrophil chemotaxis and inhibits formation of hematopoietic cells important for tumor surveillance.<sup>[33]</sup> Shapiro *et al.*, has shown that N<sub>2</sub>O exposure is a potent stimulator of liver metastasis.<sup>[34]</sup> However, the effect of N<sub>2</sub>O on colorectal carcinoma recurrence was not found to be statistically significant.<sup>[35,36]</sup>

### Opioids

Opioid administration, both perioperative and long-term, has been shown to suppress cell-mediated and humoral immunity. The suppression is naloxone reversible. Page *et al.*,<sup>[37]</sup> while evaluating the duration of opioid exposure on tumor promotion in an animal model, observed that perioperative, especially preoperative administration of morphine has favorable effect on tumor free survival. Although complex and controversial, morphine seems to exert its tumor promoting effects via:

1. Promotes apoptosis in lymphocytes and macrophages by activation of the enzymes involved in apoptotic cell death.
2. Affects NO release and inhibits cell adhesion.
3. Decreases the intracellular concentrations of cyclic adenosine monophosphate (AMP)

4. Inhibits binding of NF- $\kappa$ B.
5. Increases angiogenesis by activating cyclooxygenase (COX)-2, reciprocal transactivation of VEGF receptors, and production of prostaglandin (PG)-E2.
6. Stimulates tumor cell migration and proliferation *in vitro*.<sup>[38]</sup>
7. Suppresses NK cell cytotoxicity.
8. Promotes tumor metastasis and invasion by increased secretion of urokinase like plasminogen activator.<sup>[39]</sup>

However, morphine has not been shown to be tumor promoting in all models of study.

Mu opioid receptors (MOR) are expressed on cell lines of various tumors. Reduced tumor metastasis and growth were observed after inactivating the MOR by 'knockout technique'<sup>[40]</sup> or by treatment with MOR antagonist 'methylnaltrexone'. Mild MOR agonist tramadol also has noradrenergic and serotonergic activity. It stimulates NK cell activity. In a rat model, tramadol has been shown to block the enhancement of lung metastasis induced by surgery.<sup>[41]</sup> Morphine (10 mg) and tramadol (100 mg) were compared in hysterectomy patients for uterine carcinoma. T-lymphocyte proliferation was found to be depressed in both the groups, but remained so only in the morphine group.<sup>[42]</sup> Some studies showed fentanyl to be a suppressor of NK cell cytotoxicity<sup>[43]</sup> and some showed equivocal results. Sufentanil and alfentanil were observed to produce inhibitory effects on leukocyte migration, NK cell activity, and mitogen-induced lymphocyte proliferation.<sup>[44]</sup>

### Nonsteroidal anti-inflammatory drugs (NSAIDs)/COX2 inhibitors

COX-2 inhibitors have antitumor and antiangiogenic properties. Celecoxib inhibits morphine-induced promotion of angiogenesis, tumor growth, and metastasis.<sup>[45]</sup> Breast cancer cells overexpress COX-2 receptors. Women on long-term COX-2 inhibitors may have a lower incidence of breast cancer.<sup>[46]</sup> A large prospective study analyzing 2.5 million patient years demonstrated that use of COX inhibitor was associated with one-fifth reduction in cancer recurrence. A beneficial trend without statistical significance was observed with COX-2 inhibitors in the prevention of recurrence after colon surgery. There is emerging evidence of the benefit of propofol as a COX-2 inhibitor itself. Retsky *et al.*,<sup>[47]</sup> suggested that NSAID, given as a single dose during surgery, may also significantly reduce cancer recurrence after surgery. They reviewed 319 consecutive patients following mastectomy for breast cancer over a 4.5-year period. Fifty-five percent of the patients were given ketorolac intravenous (IV) immediately before skin incision. Cancer recurrence was 6% in the ketorolac group compared to 17% in nonketorolac group. Recent studies have suggested that COX-independent pathways may also contribute to the anticancer actions of COX-2-selective NSAIDs. Apart from its primary analgesic role,

COX-2 inhibitors reduce the amount of opioids consumed for optimal pain relief, and thereby reduce the favorable effects of opioid on oncogenesis.

### Alpha-2 agonists

Certain tumor cell lines express  $\alpha_2$  adrenoceptors on their surface. Stimulation of the receptor by agonists (clonidine, dexmedetomidine) was shown to stimulate proliferation of tumor cells on top of their NK cell modulating activity.

### Beta receptor antagonists

Peripheral  $\beta$ -adrenergic stimulation can suppress NK cell function.<sup>[23]</sup> Use of perioperative  $\beta$  blockade has been shown to halve the metastasis rate in animal model.<sup>[48,49]</sup> Hypertensive patients on chronic beta blockade were shown to have reduced rates of cancer recurrence, distant metastasis and a longer disease free interval. Other possible mechanisms might be a reduction in VEGF secretion and surgical stress response.

### Local anesthetics and regional anesthesia

The cytotoxic effects of local anesthetics correlate with their potency and lipophilicity.<sup>[50]</sup> Sakaguchi *et al.*, observed antitumor effect of lidocaine using human tongue cancer cells.<sup>[51]</sup> The possible mechanisms may be:

1. Alteration of DNA methylation of cancer cells.
2. Reactivation of tumor suppressor genes.
3. Direct cytotoxic effect.
4. Direct inhibitory effect on the epidermal growth factor (EGF) receptor.
5. Reduced mesenchymal stem cell proliferation.

Regional anesthesia *per se* can attenuate cancer recurrence by several mechanisms:

1. Decreased neuroendocrine stress response of surgery as indicated by the suppression of the rise in serum cortisol level.
2. Reduced need for general anesthesia.
3. Reduced opioid consumption.
4. Maintains NK cell, lymphocyte, and monocyte activity.
5. Perioperative pain management is superior when regional anesthesia is performed.

Retrospective studies support benefit of regional analgesia in breast, colon, or prostate cancer in terms of reduction of tumor recurrence. A large retrospective analysis<sup>[52]</sup> involving patients with invasive prostatic carcinoma who underwent open radical prostatectomy showed 57% reduction in incidence of biochemical cancer recurrence with epidural analgesia plus general anesthesia group compared to opioid analgesia plus general anesthesia group (follow-up interval of 2.8-12.8 year). In another study,<sup>[53]</sup> a four-fold reduction in recurrence and metastasis

was observed in the combined general and paravertebral analgesia group compared with general anesthesia and opioid analgesia group for primary breast cancer surgery during a follow-up of 32 months. Wada *et al.*, using a rat model<sup>[54]</sup> demonstrated that both sevoflurane general anesthesia and laparotomy suppress tumoricidal function in liver mononuclear cells and spinal anesthesia attenuated this undesirable effect. Fewer liver metastases in the sevoflurane plus spinal anesthesia group were observed in comparison to the sevoflurane group alone. Serum from patients following propofol/paravertebral anesthesia could inhibit proliferation of estrogen receptor-negative breast cancer cells *in vitro*.<sup>[55]</sup> However, contradictory reports are also plenty in the literature.<sup>[56]</sup> In a recent report, Binczak *et al.*, retrospectively analyzed 132 patients of abdominal malignancy and failed to observe any beneficial role of epidural analgesia on cancer free survival.<sup>[57]</sup>

### Blood transfusion

The requirement for blood transfusion in cancer patients can be associated with inferior survival.<sup>[58]</sup> Both anemia and blood transfusion are not desirable in the management of cancer patients.<sup>[59]</sup> Caro *et al.*,<sup>[60]</sup> demonstrated that anemia is associated with increased postoperative morbidity and mortality in all forms of cancer. On the other hand, transfusion causes a reduction in T-helper and NK cell count and IL-2, IFN- $\gamma$  levels.<sup>[61-63]</sup> Transfusion-associated immunomodulation (TRIM) is independent of whether the blood is allogenic, autogenic, or leukodepleted. Age of the blood product used might be also important as a link between cancer progression and aged erythrocytes as was recently demonstrated.<sup>[64]</sup> Perhaps factors influencing the need for blood transfusion have a greater bearing on prognosis than the transfusion of blood itself. It is important to optimize the patient before surgery and all attempts should be made to control blood loss and use blood products judiciously.

### Perioperative hypothermia

Hypothermia as mild as 35.5°C was shown to compromise cell-mediated immunity. Moderate hypothermia of 30°C suppresses NK cell activity and resistance to metastasis. As a stress response, hypothermia stimulates the sympathetic system and increases glucocorticoid release. Blood loss also increases with hypothermia and predisposes patients to blood transfusions and its immunomodulatory effects.

### Steroids

Glucocorticoids influence immune cell trafficking to sites of inflammation and causes a shift from cellular to humoral type immune responses.<sup>[65]</sup> They also inhibit the production of inflammatory cytokines (except IL-6) and their effects on



target tissues. On the contrary, production of acute phase reactants by the liver is potentiated by glucocorticoids. So, glucocorticoids can be considered to be ‘immunomodulatory’, rather than immunosuppressive agents.

### Statins

Statins have been shown to reduce various cancer incidences in humans. Possible mechanisms<sup>[66]</sup> can be:

- a. Inhibition of tumor cell growth.
- b. Antiangiogenic effect
- c. Inhibition of proliferation and induction of apoptosis in malignant cells.
- d. Repression of metastasis.

### Potential role of immunotherapy

Preoperative IFN $\alpha$  and  $\beta$  attenuates the inhibition of NK cell cytotoxicity due to surgery and anesthesia.<sup>[67]</sup> Perioperative immunotherapy may be an exciting avenue in the near future.

### Postoperative Period

Major surgery suppresses cellular immunity for several days. The pearls of optimal postoperative management of cancer patients should be maintenance of normothermia, optimal hematocrit, thromboprophylaxis, nutrition, and hydration. Pain activates the HPA axis and the sympathetic nervous system. Optimizing postoperative pain management preferably by a regional analgesia technique combined with other modalities attenuates the postsurgical inhibition of host antitumor defense mechanisms. There is no information in the literature guiding the perioperative fluid therapy in cancer patients *per se*.

### Is it time that we change our practice?

From the available evidence, it appears that perioperative management may have a role on long-term cancer free survival. Whether this dictates a change in our current anesthesia technique is a matter of controversy because of the multifactorial nature of oncogenicity. On reviewing the current literature, we can suggest to modify our practice more towards proper preoperative anxiolysis, use of ‘safer’ drugs like propofol, tramadol, NSAIDs, and use of regional analgesia wherever possible along with adequate pain control. In the words of Kurosawa and Kato,<sup>[68]</sup> “*Clinical anesthesiologists should select anesthetics and choose anesthetic methods with careful consideration of the clinical situation and the immune status of critically ill patients, in regard to long-term mortality, morbidity, and the optimal prognosis*”. In our institute which caters to approximately 7,000 oncosurgeries per year, we are trying to follow the same and are in the process of formulating a comprehensive institutional oncoanesthesia protocol based on current evidences. Whether these will help our patients, only data from long-term follow-up reports will tell.

### Conclusion

The field of perioperative immunomodulation and tumor recurrence is a new discovery. Owing to its multifactorial nature, no clear-cut guideline or practice advisory has been formulated till now regarding the conduct of perioperative period. It is impossible to separate the individual effects of anesthesia, surgery, and other perioperative interventions on the immune response. The results of the available large scale studies should be interpreted cautiously as there is no clear indication whether a simple change in anesthetic practice could affect patient survival in long-term. To what extent immunomodulation affects tumor recurrence is also a matter of speculation. Not much data is available regarding the duration of exposure and dosing of anesthetic agents necessary to produce the deleterious effects. However, we feel that we can at least incorporate whatever information available till now into our practice of oncoanesthesia and follow a working protocol till more national and international guidelines are available. This is important because in the already gloomy prognostic scenario of a cancer patient, every positive contribution, however small, helps. To conclude, a thorough knowledge of tumor oncogenesis, stress response and factors in our perioperative microenvironment which are potentially immunomodulatory is essential for the successful conduct of evidence based oncoanesthesia.

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