

Effect of Opiates, Anesthetic Techniques, and Other Perioperative Factors on Surgical Cancer Patients

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ABSTRACT

Background: Opioid pharmacotherapy is often used to treat cancer pain. However, morphine and other opioid-like substance use in patients with cancer may have significant adverse consequences, including the suppression of both innate and acquired immune responses. Although studies have examined the possibility that regional anesthesia attenuates the immunosuppressive response of surgery, the effects of morphine and other opioid-related substances on tumor progression remain unknown.

Methods: This article presents an evidence-based review of the influence of opioids and anesthetic technique on the immune system in the context of cancer recurrence. The review focuses on the field of regional anesthesia and the setting of surgical oncologic procedures. The method for perioperative pain management and the technique of anesthesia chosen for patients in cancer surgery were explored.

Results: General anesthetics have been indicated to suppress both cell-mediated immunity and humoral immunity. Evidence suggests that intravenous opioids suppress the immune

system. However, the mechanisms by which anesthetics and analgesics inhibit the immune system are not understood. Compared with the alternatives, regional analgesia offers reduced blood loss and superior postoperative analgesia. Because of these advantages, the use of regional analgesia has increased in oncologic surgeries.

Conclusion: Immune responses from all components of the immune system, including both the humoral and cell-mediated components, appear to be suppressed by anesthetics and analgesics. The clinical anesthesiologist should consider these factors in the application of technique, especially in cancer surgery.

INTRODUCTION

Cancer and control of cancer-related pain are major public health problems worldwide. In the United States, 1 in 4 deaths is related to cancer.¹ According to the American Cancer Society (ACS), an estimated 1,665,540 new cancer cases and 577,190 deaths from cancer are projected to occur in the United States in 2014.¹ The ACS projects that the majority of new cancer cases diagnosed will be cancer of the digestive system (289,610), lung/bronchial system (242,550), breast (235,030), and prostate (233,000).¹

Many treatments are available for cancer, including surgical resection, chemotherapy, radiation, immunotherapy, and various pharmacotherapies. For many cancers, early detection can result in a decrease in cancer recurrence and metastasis.¹ Because of current diagnostic and therapeutic advances, many cancers are now surgically resected at earlier stages compared with years past when these same tumors would not have been identified until after they had further grown and spread.

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Keywords: Analgesics–opioid, anesthetics, immunosuppression, neoplasms

The authors have no financial or proprietary interest in the subject matter of this article.

Table 1. Anesthetics and Effects on Immune System of Hosts

Drug	Demonstrated Immunosuppressive Effect	
	Human Model	Animal Model
Ketamine	Not investigated	Reduction of both NK cell activity and NK number
Thiopental	Not investigated	Reduction of both NK cell activity and NK number
Propofol	Not investigated	Reduction of NK cell number
Volatile agents	Reduction of NK cell number	Inhibition of interferon stimulation of NK cell cytotoxicity
Nitrous oxide	Not investigated	Acceleration in development of lung and liver metastases
Local anesthetics	Inhibition of epidermal growth factor receptor and tumor cell proliferation in vitro	Not investigated
Morphine	Inhibition of cancer cell growth	Inhibition of cellular immunity
	Inhibition of NK cell activity	Inhibition of NK cell activity
Fentanyl	Inhibition of NK cell activity	Not investigated
Tramadol	Stimulation of NK cell activity	Stimulation of NK cell activity
COX-2 inhibitors	Not investigated	Antiangiogenesis and antitumor effects

COX-2, cyclooxygenase-2; NK, natural killer.

(Table reprinted and modified from Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. *Br J Anaesth*. 2010 Aug; 105(2):106-115 by permission of Oxford University Press.)

Opioid pharmacotherapy has been a mainstay in the treatment of cancer pain. Morphine and related opioids are often used during the perioperative period. However, these substances may have significant potential adverse consequences for cancer patients given their immunological influences. Specifically, some evidence demonstrates an opioid-mediated suppression of innate immune responses and acquired immune responses. This suppression may lead to a decreased resistance to infection and may expedite the progression of cancer in patients who take opioids.^{2,3} Further, the effect of opioids on the immune system may be of particular clinical relevance in certain select populations, including elderly or immunocompromised patients.⁴ The effects of regional anesthesia on the immune system in the context of cancer recurrence have not been extensively studied.

In this article, we present an evidence-based review of the influence of opioids and anesthetic technique on the immune system in the context of cancer recurrence. We focused our review on the field of regional anesthesia and the setting of surgical oncologic procedures.

OPIOID-MEDIATED IMMUNOLOGIC EFFECTS

The administration of morphine and other opioid agents for both acute and chronic situations produces a decrease in cellular immunity as demonstrated in human cells and in animal cells.⁵⁻⁷ Both preclinical and clinical studies have shown the immunomodulatory effects of morphine.⁸ A faster progression of cancer and an increased susceptibility to infection

have been associated with the use of morphine in cancer patients.⁹ Intravenous opioids such as morphine, codeine, and fentanyl, along with volatile anesthetics such as isoflurane, have demonstrated immunosuppressive properties that include suppression of natural killer (NK) cells.⁷ NK cells are vital to the rejection of tumor cells and to the eradication of viruses. In both in vivo animal studies and in vitro human studies, intravenous opioids have been shown to decrease NK cell cytotoxicity (NKCC).^{3,4} The exact effect of opioid-mediated immunosuppression depends on the agent. Just as morphine-, codeine-, and fentanyl-mediated immunosuppressive effects have been substantiated in animal models, the partial agonist buprenorphine appears to have a more favorable immune profile devoid of intrinsic immunosuppressive activity.⁴

ANESTHESIA AND ANALGESIA EFFECTS

The effects of anesthesia and analgesia on cellular immunity are outlined in Table 1.¹⁰ The endeavor to isolate these anesthesia effects for scrutiny has presented challenges because major surgery itself has a suppressive effect on cellular immunity as outlined in Table 2.¹¹ The change in cellular immunity may stem from the invasive nature of surgery.¹⁰

Researchers have measured the anesthesia and analgesia substances eliciting a certain immune response and have used fluctuations of specific cytokines—interleukin (IL)-2, IL-10, IL-12, and interferon gamma (IFN- γ)—as a measure for immunosuppression.¹⁰ The effects of anesthesia and analgesia

Table 2. Surgical Factors That Lead to Immunosuppression, Proposed Mechanisms, Examples

Surgical Factor	Proposed Mechanism	Example
Tumor handling and disruption	Release of tumor cells into circulation	Postoperative increase in circulation of tumor cells
Decrease of circulation of antiangiogenic factors	Release of factors by primary tumors/removal of tumor prevents release	Secretion of both angiostatin and endostatin (both antiangiogenic) by tumor
Postoperative augmentation of growth factors into systemic and local circulation	Support of metastasis	Postoperative increase of vascular endothelial growth factor and epidermal growth factor
Perioperative immunosuppression due to surgery	Suppression of cellular immune system; loss of tumor surveillance protection	Reduction in number of natural killer cells, cytotoxic T lymphocytes, dendritic cells, and T-helper cells in circulation

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on cellular immunity have been studied in vitro, in certain animal models, and in humans.¹⁰

Intravenous Anesthetic Agents

Melamed et al investigated the effect of intravenous anesthetic agents on cellular immunity.¹² They injected rats with tumor cells and subsequently subjected the animals to different anesthetic agents. Rats treated with ketamine had 5.5 times the number of tumor cells of control rats. Rats treated with thiopental had 2 times the number of tumor cells of control rats. Melamed et al also found that ketamine, thiopental, and propofol treatments suppressed NK cell activity and NK cell levels compared with the controls. They found a correlation between the number of viable tumor cells present at autopsy and NK cells in the aggregate of the groups but not in the individual groups.

The link between docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and the low incidences of several strains of cancer has also been investigated. Siddiqui et al tested propofol-docosahexaenoate (propofol-DHA) and propofol-eicosapentaenoate (propofol-EPA) for their effects on the migration, adhesion, and apoptosis of MDA-MB-231 breast cancer cells.¹³ The propofol conjugates inhibited cellular adhesion, migration, and apoptosis in MDA-MB-231 breast cancer cells.

Inhalational Agents

Halogenated volatile anesthetics have been shown to have properties of immunomodulation and to suppress the function of NK cells.^{7,14} Specifically, isoflurane and halothane each attenuate the interferon stimulation of NKCC in mice.^{7,10} In addition, 1 in vitro investigation has yielded results that warrant

further investigation of the effects of inhalational agents on immunosuppression.¹⁵ This study has demonstrated that sevoflurane administration leads to the altered release of cytokines such as IL-1 β and tumor necrosis factor (TNF)- α by NK and NK-like cells.¹⁵

The identification and characterization of the immunosuppressive effects of inhalational agents has been challenging for researchers because of the many variables in the conditions of inhalational anesthesia administration and the different drugs to which patients are exposed.¹⁰ In a large retrospective analysis, Schlagenhauff et al found a relationship between anesthesia and cancer survival rate: compared with the use of local anesthesia, general anesthesia was associated with a decreased survival rate for patients with primary melanoma excisions.¹⁶

Another study indicated that general anesthesia leads to the reduced circulation of NK cells in patients undergoing elective orthopedic surgery.¹⁷ Also, previous literature has suggested an association between cancer surgery and the systemic release of tumor cells and micrometastases.¹⁸ Further research has yielded data from both in vitro evaluations and in vivo animal studies that indicate impairment of neutrophils, macrophages, dendritic cells, and T cells with the use of anesthesia for cancer surgery.¹⁸

Nitrous Oxide

The toxicity of nitrous oxide has been demonstrated. Nitrous oxide disrupts the process of DNA synthesis and depresses neutrophil chemotaxis. Additionally, nitrous oxide administration is associated with both depressed neutrophil function and reduced mononuclear cell production.¹⁹

The mouse model has revealed the possibility of immunosuppression from nitrous oxide administration; Shapiro et al demonstrated that nitrous oxide exposure is associated with the accelerated development of lung and liver metastasis.²⁰

Nitrous oxide has also been examined for its effects on humans.^{21,22} Nitrous oxide exposure may increase bowel distension in patients who are subject to elective colon resection.²³ However, further investigation has led to the interpretation that nitrous oxide does not increase the incidence of surgical wound infection.²¹ In addition, a follow-up of a randomized controlled trial indicated that nitrous oxide may not increase the risk of cancer recurrence after colorectal surgery.²²

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs lead to the attenuation of prostaglandin synthesis by inhibiting the cyclooxygenase (COX) enzyme.¹⁰ Furthermore, tumor cells have been shown to secrete prostaglandins, and researchers have explored the possibility that the ability to secrete prostaglandins may be a mechanism to evade the immune response.²⁴

The rat model has demonstrated that COX-2 inhibitors possess both antitumor and antiangiogenic properties.²⁵ Benish et al elucidated the relationship between COX-2 inhibitors and immune suppression.²⁶ They found that postoperative immunosuppression may stem from the excess release of prostaglandins and catecholamines.

The work of Farooqui et al was undertaken to determine if celecoxib prevents morphine-induced tumor growth without compromising analgesia.²⁷ They found that celecoxib thwarts the morphine-induced stimulation of COX-2, PGE₂, angiogenesis, tumor growth, metastasis, and mortality and that celecoxib achieves these preventive actions without the attenuation of analgesia.

Local Anesthetics

The effects of local anesthetics on tumor suppression have been studied in cells.¹⁰ Lidocaine seems to exert an antitumor effect.²⁸ Ropivacaine seems to exert a suppressive effect on the growth of tumor cells.²⁹

Lidocaine possibly exerts its antiproliferative effect on tumors through the epidermal growth factor receptor (EGFR).²⁸ An experiment was structured such that lidocaine was administered in clinical concentrations to tongue cancer cells with the concurrent evaluation of EGFR levels of activity.²⁸ The clinical concentration of administered lidocaine led to the marked decrease of EGFR-induced proliferation of tongue cancer cells and to the

inhibition of the EGFR-stimulated tyrosine kinase activity that stimulates EGFR.²⁸

The effect of ropivacaine on cancer cell growth has been studied *in vitro*.²⁹ Ropivacaine seems to suppress the growth of human colon adenocarcinoma cells and has been demonstrated to inhibit cancer cells in a dose-dependent manner.²⁹ Although more research is needed to elucidate the effects of local anesthetics on cancer cell growth, these studies show promise for optimized approaches.

OTHER FACTORS' EFFECTS

Regional Anesthesia

More studies on the effect of regional anesthesia on immunosuppression are needed. To date, most of the studies on the effect of regional anesthesia on immunosuppression are retrospective. One study examined the incidence of biochemical cancer recurrence in 2 treatment groups after open prostatectomy under general anesthesia.³⁰ One group received open prostatectomies with epidural analgesia and the other group was given postoperative opioid analgesia. The group with epidural analgesia had a 57% reduction in cancer recurrence compared to the opioid group.

An investigation by Wada et al explored the possibility that general anesthesia may improve the overall treatment of cancer.³¹ In a rat model, sevoflurane general anesthesia and laparotomy each suppressed tumoricidal function in liver mononuclear cells, and spinal block attenuated this suppressive effect. The Wada et al study also explored the possibility that the combined administration of sevoflurane and a spinal block may reduce the promotion of tumor metastasis.

Regional anesthesia may exert an effect on breast cancer metastasis. In one investigation, serum samples were taken from breast cancer surgery patients who experienced various anesthetic techniques.³² These samples were studied for breast cancer cell function *in vitro*, and the results indicated a possible link between anesthetic technique and breast cancer cell function.

Regional anesthesia influences the long-term outcome of cancer surgery in 3 ways.^{10,18} First, regional anesthesia may attenuate the intrinsic immunosuppression from surgery.³³ Second, patients who receive regional analgesia often do not need as much opioid treatment, and as a result, tend to avoid the immunosuppressive effects that accompany opioid treatment.³⁴ Third, the combination therapy of regional and general anesthesia leads to a reduction in the dose of inhalational anesthetic required. This decrease in the required dose can

potentially affect long-term outcome from cancer-related surgery.¹⁰

Acute Pain

The conventional understanding holds that acute pain exerts a suppressive effect on NK cell activity.^{35,36} The rat model has been used to demonstrate that different pain management techniques may have varying effects on host immunity, including antitumor defense mechanisms. In a study by Page et al, the suggestion that postoperative pain somehow mediates tumor production was examined by comparing the effects of 2 regimens of analgesia for postoperative pain in rat tumors after surgery: systemic fentanyl and intrathecal administration of bupivacaine and morphine.³⁷ The surgery-induced increase in lung tumor retention was attenuated by >65% in the rats treated with fentanyl and by >45% in the rats treated with the bupivacaine/morphine regimen. In addition, fentanyl had a suppressive effect on NK activity. Whether these data reflect a more significant clinical relevance of morphine-induced cancer progression vs fentanyl-induced cancer progression is uncertain.

The nature and effects of acute pain challenge the elucidation of the influence of opioids on the immune system.¹⁰ Opioids possibly improve cancer resistance in postoperative pain in vivo, exert an immunosuppressive effect when administered at a basal level, and may exert different effects on the immune system during different states of pain.³⁸

Blood Transfusion

Blood transfusions may support metastasis.^{10,39} Allogeneic blood, or transfusion-associated immunomodulation, has an immunosuppressive effect.⁴⁰ This effect has been substantiated both in vivo and in vitro.⁴¹⁻⁴³

Blajchman et al examined the possibility that blood transfusions may exert adverse effects on cancer patients.⁴³ Using rat, mouse, and rabbit models, they compared the effects of allogeneic blood transfusion with the effects of leukodepleted allogeneic blood transfusion. Animals that received the allogeneic blood transfusion experienced a significant increase in metastatic pulmonary nodule growth.

Chen et al compared the effects of allogeneic blood transfusion and autologous blood transfusion in cancer patients.⁴⁴ Both transfusion types resulted in a decrease in IFN- γ , T-helper cells, and the T-helper/cytotoxic T-cell ratio. The levels of these substances remained low in patients who received allogeneic blood transfusion when measured 5 days after operation. The levels of these substances were

maintained in patients who received autologous blood transfusion.

Immunotherapy

Rats pretreated with an IFN inducer have been shown to experience an increase of NK cell activity and a dampened immunosuppression induced by fentanyl.⁴⁵ Colacchio et al found that pretreatment of rats with IFN may dampen the NK cell inhibition that is normally associated with surgery and anesthesia.⁴⁶ The study also showed that treatment of mice with low-dose IL-2 and ketorolac leads to a reversal of NK cell-mediated immunosuppression. This immunosuppression is highly associated with surgery. In addition, Colacchio et al demonstrated that morphine enhances the NK cell-mediated immunosuppression from surgery.

Ben-Eliyahu has considered the effect of surgery on cancer, specifically whether surgery promotes metastasis.⁴⁷ He is also credited with proposing that immunotherapy yields improved results when administered during the perioperative period.

Hypothermia

Hypothermia has been studied in rats for its suppression of NK cell activity.⁴⁸ The rat model has also been used to demonstrate that hypothermia may suppress resistance to metastasis.⁴⁸ Melamed et al suggested that the extent of hypothermia, namely the rat's temperature (with hypothermia exposures of 33°C-35°C for 1 hour), influences immunosuppression.¹²

Hypothermia is a common surgical complication and has been suggested as a cause of other surgical complications. Ben-Eliyahu et al examined the immunosuppressive effect of hypothermia in 2 groups of rats.⁴⁸ One group was hypothermic and another group was normothermic. Each group was injected with tumor cells, and the blood of each group was monitored for NK cell activity. Tumor retention was increased by 250% in the hypothermic group compared with the normothermic group. In addition, metastasis increased up to fourfold in the hypothermic group compared with the normothermic group.

Anxiety

Studies indicate that anxiety both suppresses the immune system and creates an environment that supports cancer growth.¹⁰ Experiments with rat models have indicated that stress has a suppressive effect on NK cell activity and a retentive effect on lung tumor growth.⁴⁹ Human studies have explored how psychological stress contributes to immunosuppression.⁵⁰

Stefanski et al examined the effects of stress on the immune system, measuring both NK cell activity and lung tumor retention.⁴⁹ Rats were injected with tumor cells, and pretreatment with the beta-adrenergic antagonist butoxamine significantly influenced stress, NK function, and distribution, suggesting a mediation or modulation linked to an adrenergic mechanism.

Andersen et al examined the effect of chronic stress on cellular immune responses in patients during the periods of breast cancer diagnosis and breast cancer surgery.⁵⁰ In their examination of 116 patients who had been treated surgically for invasive breast cancer, stress served as a significant predictor of lowered NK cell lysis, the NK cell response to recombinant IFN- γ , and the proliferative response of peripheral blood lymphocytes to different proteins.

BASIC SCIENCE FINDINGS RELATED TO NEURAXIAL AND REGIONAL ANESTHESIA

Reduced blood loss, decreased need for blood transfusion, superior analgesia, and increased mobility have all been cited as advantages of regional anesthesia over systemic opioids.⁵¹⁻⁵³

In addition, neuraxial and regional anesthesia and analgesia provide a substantial reduction in postoperative pain, intravenous opioid use, and volatile anesthetic requirements. Both the attenuation of the surgical response and the inhibition of the immune response as a result of the use of either epidural analgesia or anesthesia have been documented in a study by Hong and Lim.⁵⁴ Only a few studies have been published that demonstrate the effect of neuraxial and regional anesthesia on the immune system. Even fewer studies explore the effect of neuraxial and regional anesthesia on the immune system and cancer recurrence.

Studies have illustrated the effects of regional anesthesia on cytokine serum levels IL-2, IFN- γ , IL-10, and plasma epinephrine/cortisol.^{55,56} Plasma levels of cortisol and epinephrine were shown to be significantly decreased in the regional anesthesia group. IFN- γ also was shown to increase as a result of the administration of regional anesthesia. A measurement of T-helper cells and lymphocytes revealed that the regional anesthesia group had significantly higher numbers of T-helper cells and lymphocytes post-operation compared to the group without regional anesthesia. Another in vitro study of 32 people demonstrated the effect of regional anesthesia on TNF- β and vascular endothelial growth factor (VEGF).⁵⁷ TNF- β and VEGF are important markers for inflammation. Although the sample group in this study was small, in terms of the effect of regional

anesthesia, it illustrated both a postoperative fall in VEGF and also a postoperative increase in TNF- β .

Both of these in vitro studies share a theme that merits further study: regional anesthesia attenuates the immunosuppressive response to surgery.^{14,54,56,58} Different studies^{58,59} conflict with regard to the effects of morphine on tumor progression. One study demonstrated that morphine treatment leads to a reduction in colon adenocarcinoma cells.⁵⁹ Different receptors for endogenous and exogenous opioids possibly cause divergent effects for in vivo animal studies and in vitro assays.⁶⁰

Normal volunteers have also shown that morphine administration leads to the suppression of antibody-dependent cell cytotoxicity.⁶¹ However, the effect of morphine on NK and B cells remains unknown. Possible mechanisms by which morphine exerts its effects are explored in Figures 1 and 2, reprinted from Gach et al.¹¹

The opioid-cancer recurrence associations found in animal studies and in human in vitro studies have increased interest in the use of regional anesthesia and analgesia in patients with cancer. In the past decade, several retrospective trials have shown mixed results regarding the relationship between opioids and the stimulation of both metastasis and immunosuppression.⁵⁸

CLINICAL SCIENCE FINDINGS

Ovarian Cancer

A retrospective study by de Oliveira et al analyzed 182 patients who underwent cytoreductive ovarian debulking.⁶² Patients who had <1.0 cm of their tumors remaining were evaluated. Time to recurrence (defined as cancer antigen [CA]-125 >21 u/mL) was the primary endpoint of the study, and time to death was the secondary endpoint. Each patient in the study received general anesthesia; none received regional anesthesia alone. Induction was performed with fentanyl 2-3 mcg/kg, midazolam 0.02-0.04 mg/kg, and propofol 1.5-2.5 mg/kg. Sevoflurane was the inhalation agent used during the maintenance of anesthesia.

Patient health records were analyzed for 3-9 years and were stratified into 3 groups. In 1 group, 127 patients received neither epidural anesthesia nor analgesia. In another group, 26 patients received epidural anesthesia/analgesia intraoperatively as part of a balanced anesthetic technique and for postoperative pain control. In another group, 29 patients received epidural anesthesia/analgesia for postoperative pain control only. The variation in group sizes deserves emphasis; 127 patients received only intravenous opioids for intraoperative and postoper-

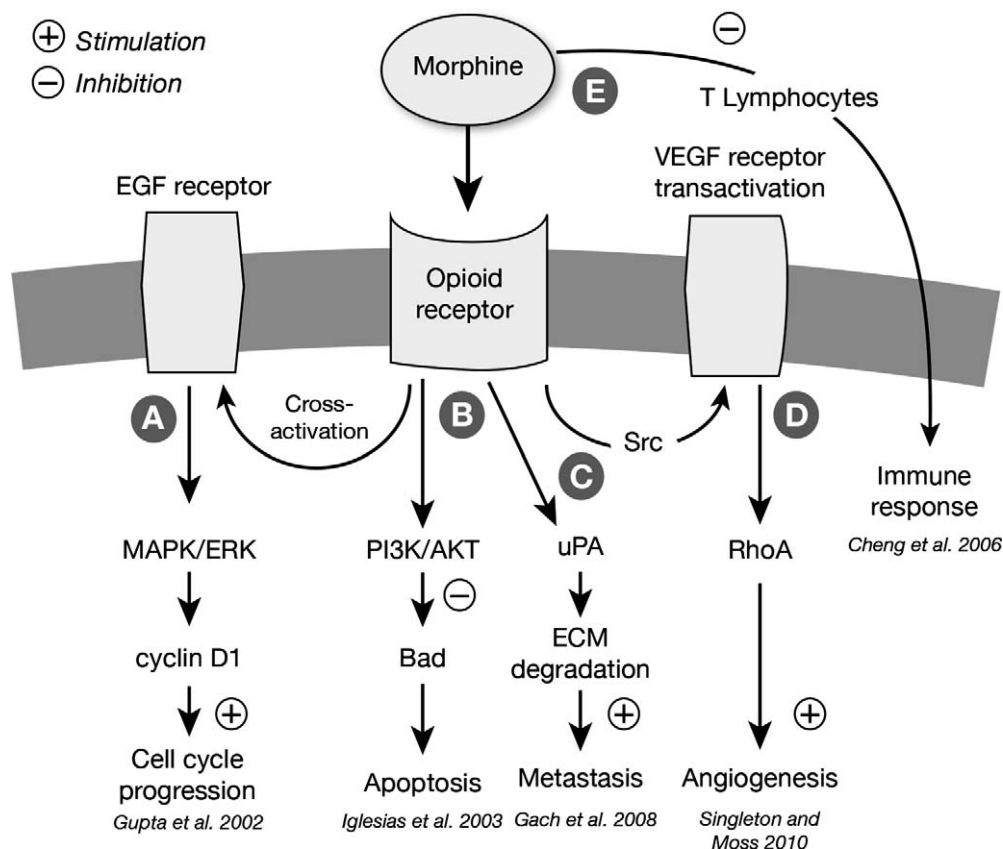


Figure 1. Possible mechanisms of the opioid receptor–mediated influence of morphine on tumor growth. Morphine binds to the μ -opioid receptor and (1) stimulates the mitogen-activated protein kinase (MAPK) signaling pathway via the G protein-coupled receptors/extracellular-signal-regulated kinase (ERK) pathway, resulting in cell cycle progression; (2) activates the phosphatidylinositol 3-kinase/AKT (PI3K/AKT) pathway, mediating antiapoptotic effects through the Bcl-x_L/Bcl-2-associated death promoter protein; (3) upregulates urokinase plasminogen activator (uPA) expression and secretion promoting extracellular matrix (ECM) degradation and metastasis; (4) transactivates vascular endothelial growth factor (VEGF) receptors and induces angiogenesis; and (5) suppresses the function of T lymphocytes, leading to immunosuppression. (Figure and caption reprinted with permission from Gach et al.¹¹) EGF, epidermal growth factor; Src, sarcoma.

active pain control, and 55 patients received epidural anesthesia/analgesia.⁶²

Both intraoperative opioid use and postoperative opioid use were measured in milligrams of morphine equivalents. Kaplan-Meier survival curves were obtained. A log-rank test was used to compare median survival time and time to recurrence between groups. The results for the group whose members received preoperative epidurals indicated an increased time to recurrence of ovarian cancer of 73 months. Results showed a decreased time to recurrence for the group whose members received no epidural of 38 months ($P < 0.001$) and an average of 33 months ($P < 0.002$) for those who received epidurals for postoperative pain control use only.⁶²

Although propensity scores were used in statistical analysis, this retrospective study suffered from a confounding variable bias. In addition, neither the operative care nor the postoperative care was standardized, particularly regarding the amount of volatile anesthetic administered and the amount of postoperative opioid administered.

Colon Cancer

Other retrospective studies on patients with colon cancer, prostate cancer, and breast cancer have yielded mixed results regarding cancer recurrence in the context of opioid analgesia/anesthesia.^{30,63-66} Gottschalk et al retrospectively initially examined 669 patients for 7 years, examining the time to recurrence of cancer in 2 groups.⁶³ One underwent

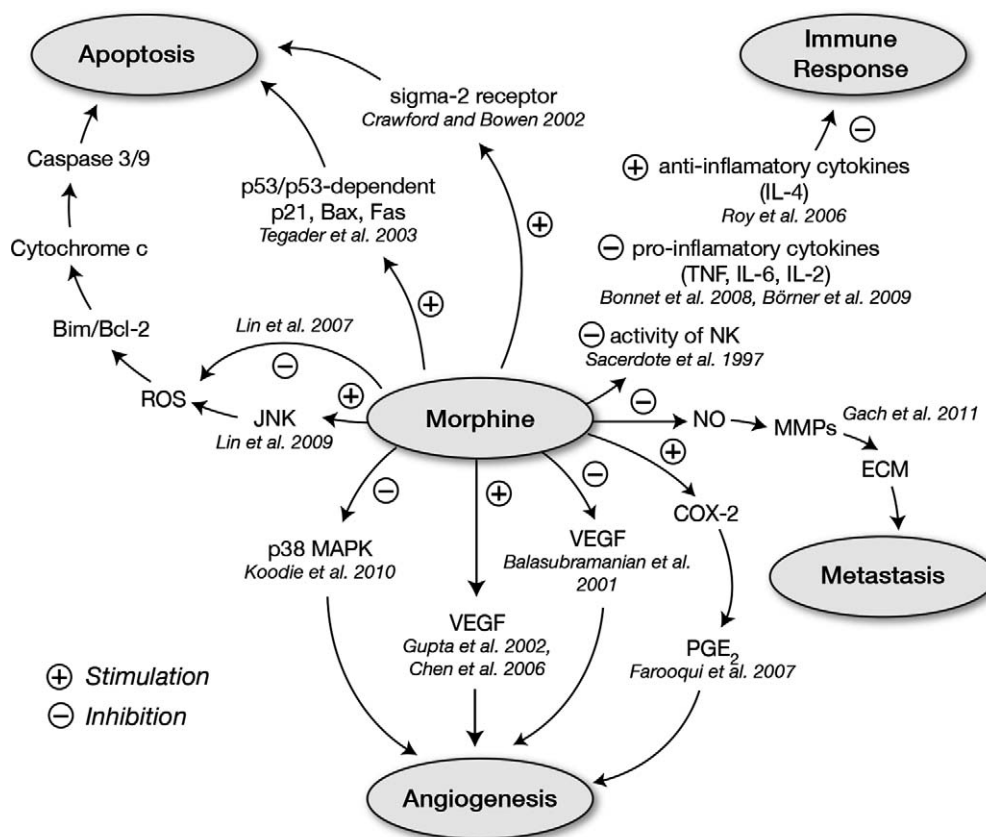


Figure 2. Possible pathways, other than through the opioid receptors, by which morphine influences cancer progression and suppression. (Figure and caption reprinted with permission from Gach et al.¹¹) Bax, bcl-2-associated x protein; Bcl-2, B cell lymphoma 2; Bim, bcl-2-interacting mediator of cell death; COX-2, cyclooxygenase-2; ECM, extracellular matrix; Fas, TNF receptor superfamily member 6; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; NK, natural killer (cells); NO, nitric oxide; PGE-2, prostaglandin E2; ROS, reactive oxygen species; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

colorectal surgery with epidural analgesia (n=256) and the other group underwent colorectal surgery with general anesthesia (n=253). The median follow-up time for this study was 1.8 years. Cancer recurrence was detected in 16% of the nonepidural therapy patients and in 13% of the epidural therapy patients. The patients who received epidural therapy shared certain characteristics. More males than females received epidural therapy. The patients who received epidural therapy generally had lower American Society of Anesthesiologists classification scores, had worse tumor grades, and received a lower fraction of inspired oxygen (FiO₂) intraoperatively. Also, the patients who received epidural therapy underwent different surgical procedures, received greater crystalloid volume, experienced higher estimated blood loss, and were more likely to receive radiation and chemotherapy.⁶³

The multivariable analysis of this study showed no association between the epidural procedure and the time to recurrence of cancer ($P=0.43$). The post-hoc analysis of 9 pairwise interactions indicated that only age showed a linear effect. Those who were older than 64 experienced better outcomes ($P=0.001$, hazard ratio of 0.67) with the use of epidurals compared to those younger than 64. Because these results are in the form of a post-hoc analysis, they could be classified as a type 1 statistical error as described by the authors.⁶³

These authors further postulated that younger patients may experience more aggressive forms of the disease and of histological tumor types. However, this retrospective study may be confounded by the lack of determination of the exact time of epidural infusion discontinuation. The article states that the median follow-up time was short and that a longer

follow-up time may have indicated more significant differences.

The study by Gottschalk et al conflicts with the Christopherson et al prospective analysis of Veterans Affairs Cooperative Study Number 345 (CSN 345).⁶⁷ CSN 345 was a multicenter prospective trial in which 1,021 randomized colon cancer patients were placed either into a general anesthesia group or an epidural anesthesia supplemented with general anesthesia treatment group. During a 30-day postoperative period, the results of the study did not indicate significant differences in death or major complications between the 2 treatment groups.

Christopherson et al further expanded upon the CSN 345 trial by recording and evaluating long-term survival statistics for patients ($n=177$) who suffered from colon cancer.⁶⁷ They employed multivariable analysis to construct log regression survival models that they used to analyze pathological stage, type of anesthesia used, and other variables. Epidural supplementation was associated with improved survival ($P=0.012$) within the first 1.46 years after the operation, but after 1.46 years, the type of anesthesia was not found to affect survival ($P=0.27$) in the patients without metastases. Epidural anesthesia had no effect on the survival of patients with metastases.

In comparing the results of the 2 studies, Gottschalk et al concluded, smaller sample size notwithstanding, that no clear difference in data in terms of variables exists in their study. The different findings of these 2 studies may be explained by the observed differences ensuing from the perioperative management of epidurals. Christopherson et al stated that their investigation was preliminary and that covariables such as cause of death merited further examination.⁶⁷

Prostate Cancer

Biki et al performed a retrospective analysis of 225 patients who underwent radical prostatectomy.³⁰ Patients were divided into 2 groups. One group was treated with general anesthesia/intravenous opioids, and the other group was treated with epidural/general anesthesia. This study used biochemical recurrence, defined as the increase in prostate-specific antigen (PSA) compared with its immediate postoperative nadir, to serve as the primary endpoint measurement. This study also charted the recurrence-free interval time, which is the time after both surgery and PSA readings at or below the postoperative nadir. The follow-up interval was 2.8-12.8 years.

The data demonstrated a lower estimated risk of recurrence for the epidural/general anesthesia group ($P<0.001$, hazard ratio of 0.34) compared with the general anesthesia/intravenous opioid group. Risk

calculations—adjusted for tumor size, Gleason score, and preoperative PSA—led to a 57% lower risk (95% confidence interval [CI] 17%, 78%) in the epidural/general anesthesia group compared with the general anesthesia/intravenous opioid group.³⁰

This study had several limitations. Because the work was a retrospective analysis, the patients were not randomized. In addition, several unaccountable confounding variables were not able to be excluded. Furthermore, the sample size was small, which may have caused a type 1 error according to the study authors.

Tsui et al conducted a retrospective analysis of 99 patients with prostate cancer who were treated with either general anesthesia alone or general anesthesia with epidural anesthesia.⁶⁸ The measured biochemical recurrence of prostate cancer was defined as a PSA score >0.2 ng/mL. The median follow-up time was 4.5 years. No difference was found between the combined epidural anesthesia/general anesthesia and the general anesthesia group ($P=0.44$).

The limitation of this study is its small sample size, which may have caused a type 2 error in the acceptance of the null hypothesis according to the study authors. Demonstration of the effects of epidural analgesia on disease recurrence rates post-radical prostatectomy requires larger randomized controlled trials.^{30,68}

Wuethrich et al published a retrospective trial concerning prostate cancer recurrence and epidural analgesia that focused on 250 patients undergoing retropubic radical prostatectomy with extended pelvic lymph node dissection.⁶⁹ The patients were assessed for various factors, including biochemical recurrence-free survival, clinical progression-free survival, and cancer-specific survival. The follow-up time was 3 years.⁶⁹

The definitions of survival varied among the measured factors. Biochemical recurrence-free survival was indicated by a PSA score ≤ 0.2 ng/mL. Cancer-specific survival was defined from operation time to death caused by tumor. Clinical progression-free survival was determined at the points of either clinical progression or death. Overall survival was defined from operation time to time of death from any cause.⁶⁹

Patients were divided into 2 groups; 1 group was treated with general anesthesia combined with epidural anesthesia and the other with general anesthesia and ketorolac/morphine analgesia. These groups showed no difference in rate of improved biochemical recurrence-free survival, cancer-specific survival, or overall survival. However, a reduction in the clinical progression of cancer was discovered ($P=0.002$, hazard ratio of 0.45 and 95% CI 0.27, 0.75).

This study is significant because all of the anesthetic techniques were standardized. However, this was also a retrospective analysis and, despite the propensity scores, the patients were not truly randomized.

Breast Cancer

Exadaktylos et al conducted a retrospective analysis of 129 patients who underwent simple mastectomy with axillary clearance during the span of 1 year.⁶⁵ The patients were divided into 2 groups. One group received general anesthesia (n=79) with postoperative intravenous morphine, and the other group received a paravertebral block (n=50) with general anesthesia. Patients who underwent wide local excision procedures and sentinel axillary lymph node procedures were excluded because these procedures did not require paravertebral blocks and were also seen as less extensive.⁶⁵

The paravertebral block was standardized among patients with a 0.2 mL/kg bolus of 0.25% levobupivacaine before the induction of general anesthesia. The infusion for each patient was scheduled for 48 hours after each operation. The same anesthetist placed all of the paravertebral catheters. The same surgeon performed all of the operations. The same oncologist cared for each patient. The same general anesthesia protocol was used for each patient.⁶⁵

Either cancer recurrence or metastasis was documented in 6% of the patients who received the block and in 24% of the patients who received only general anesthesia/intravenous morphine ($P=0.013$). Multivariable analysis also indicated that the risk of recurrence was less after the adjustment for both the histological grade and the axillary involvement ($P=0.012$, hazard ratio of 0.21 and 95% CI 0.06, 0.71). As with all the previously mentioned studies, this study is limited because it is both retrospective and nonrandomized. The authors also state that confounding variables such as tumor size, margin size, chemotherapy rates and regimes, and the amount of postoperative morphine used further limited this study.⁶⁵

Sessler et al conducted a prospective clinical trial with an enrollment of approximately 1,100 patients over the span of 5 years from 2008-2013.⁷⁰ In this trial, they compared 2 groups of breast cancer surgery patients. One group was randomized to paravertebral or high-thoracic epidural analgesia combined with sedation or light anesthesia, and the other group was given intraoperative volatile anesthesia and postoperative opioid analgesia. They compared the local or metastatic recurrence after breast cancer surgery in the 2 groups and hypothesize that the local/metastatic recurrence after breast cancer surgery is lower

with analgesia and sedation/light anesthesia than with intraoperative anesthesia and postoperative analgesia.⁷⁰

Only 1 randomized prospective trial has demonstrated the effects of regional anesthesia on long-term cancer survival.⁷¹ The trial involved 446 patients and 23 clinical sites. This study examined abdominal procedures that focus on the complete surgical excision of cancer, including esophagectomy, gastrectomy, nephrectomy, cystectomy, radical hysterectomy, and open prostatectomy.

The patient populations were divided into groups. The epidural and postoperative analgesia group consisted of 263 patients. The nonepidural and postoperative intravenous opioid-based analgesia group originally consisted of 240 patients. The primary endpoint was cancer-free survival, and the secondary endpoint was all causes of mortality. The endpoints were measured in 5-year increments for up to 15 years. Both cancer recurrence rate and the survival from date of surgery were recorded. The research staff who collected follow-up outcome data were blinded to exposure status. Each patient received standardized premedication, intraoperative monitoring, and induction and maintenance anesthesia. Each epidural catheter was inserted in the thoracic region with continuous infusions of ropivacaine supplemented with either fentanyl or meperidine. The epidurals were kept in for about 3 days postoperatively.

The median time to recurrence of cancer or death was 2.6 years in the epidural group and 2.8 years in the nonepidural group ($P=0.61$, hazard ratio of 0.95, 95% CI 0.76, 1.17). Five-year recurrence and mortality rates were comparable in predefined subgroups such as sex, age, and type of surgery in all categories (all P values >0.10).

Analysis of the data identified significant predictors of early death or recurrence of cancer. These predictors included patient age ($P<0.001$), sex ($P<0.001$, hazard ratio of 0.65, 95% CI 0.52, 0.82), and risk from red cell transfusion ($P=0.002$, hazard ratio of 0.63, 95% CI 0.47, 0.84). However, the epidural group did not show negative predictors ($P=0.72$, hazard ratio of 1.04, 95% CI 0.84, 1.3).⁷¹

This study offers the strength of a relatively large sample group, randomization, and a long follow-up period. However, the study also has limitations. The exclusion criteria were examined to detect smaller effects that might still be of considerable clinical importance, particularly for individual types of cancer. The examination revealed that the study lacked power (n=446).

As of early 2014, approximately 29 prospective clinical trials are underway. More clinical trials are

anticipated. We maintain optimism that at least 1 of these clinical trials will elucidate the effects of regional anesthesia in the context of oncologic therapy.

DISCUSSION

General anesthetics have been indicated to suppress both cell-mediated immunity and humoral immunity. Evidence suggests that intravenous opioids suppress the immune system. However, the mechanisms by which anesthetics and analgesics inhibit the immune system are not understood.

To avoid this immune suppression, the use of regional analgesia might be preferable to the use of intravenous opioids and general anesthetics. Compared with the alternatives, regional analgesia offers reduced blood loss and superior postoperative analgesia. The immunosuppressive effects of regional anesthesia and analgesia may be less than the immunosuppressive effects of either intravenous opioids or general anesthesia. Because of these perceived advantages, the use of regional analgesia has generally increased in oncologic surgeries although no hard data have been published at this time. More clinical studies are necessary to elucidate the impact of regional anesthesia on the immune system of the patient undergoing curative cancer surgery.

The effects of intraoperative and postoperative regional analgesia merit further extensive study. Also, certain factors merit further exploration: the reduction of metastasis and tumor recurrence, surgical site infection rates, and long-term survival rates.

CONCLUSION

Immune responses from all components of the immune system, including both the humoral and cell-mediated components, appear to be suppressed by anesthetics and analgesics. This suppression has been demonstrated in vitro and in vivo for both animals and humans. Although they serve to alleviate stress responses and pain, anesthetics and analgesics suppress immune function. The clinical anesthesiologist should consider these factors in the application of technique, especially in cancer surgery.

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This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care and Medical Knowledge.