Surgery for Cancer: Does Anesthesia Matter?

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As anesthesiologists, we often assume that once the immediate effects of our drugs dissipate, the body returns to the preanesthetic state without long-term sequelae. However, in addition to profound immediate effects, anesthesia can also have long-term consequences. In this issue of *Anesthesia & Analgesia*, 2 articles deal with 1 potentially devastating consequence: an increased risk of metastatic spread of malignant cells after cancer surgery. Gottschalk et al.[1] review the pathophysiology of cancer recurrence after surgery, the potential role of anesthesia on the risk of recurrence, and discuss how this might affect clinical practice. Their review is an opportune reminder that not all consequences of anesthesia disappear after the immediate postoperative period. The authors of the second article report findings from an analysis of tumor recurrence after surgery for breast cancer.[2] The results suggest that intraoperative administration of the nonsteroidal antiinflammatory drug (NSAID) ketorolac significantly decreases the incidence of cancer recurrence compared with non-NSAID analgesics.

Cancer is second only to cardiovascular disease as the most frequent cause of death among adults in the developed nations. Although cancer does occur in children and young adults, nearly 75% of cases occur in individuals aged 60 years and older, and more than one-third in those aged 75 years and older.* Populations in the developed countries are aging, with a concomitant increase in age-related diseases, including cancer. As a consequence, anesthesiologists will be confronted with increasing numbers of patients presenting for cancer surgery.

Surgical removal of a malignant tumor is the primary treatment for most cancers. However, surgical manipulation can release isolated cancer cells into the bloodstream and lymphatic system. Whether these develop into metastases depends on the balance between the patient's immune defenses and the ability of the tumor cells to seed, proliferate, and attract formation of new blood vessels. Several factors can upset this balance. The immune system, by specifically identifying and destroying malignant cells (tumor immune surveillance), is a primary defense against cancer.[3] Major surgery is associated with immunosuppression which, together with the release of cytokines, chemokines, and prostaglandins, can facilitate angiogenesis, tumor metastasis, and tumor invasion.[4] In particular, surgery inhibits the natural killer (NK) cells that are critical in limiting the spread of malignant cells.[5] They are the only cell type able to recognize and lyse cells lacking self human leukocyte antigen class I molecules. Because many tumor cells inhibit the expression of these molecules, NK cells are the major first-line defense against the development of primary tumors and the metastatic spread of established tumors.

James Cottrell defined anesthesiologists as "… doctors who keep patients alive while surgeons do things that would otherwise kill them."[6] But could our choice of anesthesia increase the risk of cancer recurrence that could kill the patient, or could a more appropriate choice of drug decrease the risk of recurrence after cancer surgery? There is increasing evidence from experimental studies and a limited number of clinical studies that some anesthetics and opioids may be contributing factors to the development of metastases after cancer surgery.[1] Inhaled anesthesia, independent of other factors, may increase the risk of malignant cells escaping from immune control. Volatile anesthetics induce apoptosis in lymphocytes, reduce NK cytotoxicity, and alter the release of cytokines by NK cells in response to tumor cells.[7] On the positive side, some anesthetics are cytotoxic to poorly differentiated human carcinoma cell lines and might help counteract the spread of cancer cells.[8] On balance, however, it would seem prudent to limit the use of inhaled anesthesia in patients undergoing cancer surgery. Gottschalk et al.[1] propose 2 alternatives: regional anesthesia and total IV anesthesia (TIVA) with propofol. Although several studies have suggested that regional anesthesia preserves immune defenses against tumor progression by attenuating the surgical stress response, most have been retrospective and have investigated regional combined with general anesthesia.[9] Propofol, the most popular hypnotic used in TIVA, attenuates the surgical stress-induced adverse immune response to surgery and has antitumor activity, possibly related to inhibition of cyclooxygenase.[10,11] Unfortunately, propofol is not a complete anesthetic and needs to be combined with an opioid when used in TIVA.

Opioids have several actions that can promote the dissemination of malignant cells. They stimulate angiogenesis, a key factor in the growth and dissemination of

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cancers, in part by activating cyclooxygenase-2 (COX-2), increasing production of prostaglandin E_2, which promotes angiogenesis and tumor progression.[12] Opioids also significantly influence the functioning of the immune system indirectly via the hypothalamic-pituitary axis and directly through opioid receptors, especially μ_3 receptors expressed on immunocytes. These receptors are involved in signaling pathways that modulate antibody production and the activity of NK cells.[13] Now, there is compelling evidence that animals, including humans, synthesize morphine and related morphinan alkaloids, and that these endogenous opioids are involved in morphinergic signaling in immune cells.[14] The μ_3 receptors are also expressed on human cancer cell lines, where they are coupled to constitutive nitric oxide release.[15] Opioid alkaloids such as morphine bind strongly to the μ_3 receptor, whereas binding of synthetic opioids such as fentanyl and the endogenous opioid peptides is considerably weaker. This explains why alkaloids such as morphine are predominantly immunosuppressive, whereas the endogenous opioid peptides are predominantly immunostimulatory.

An accepted method of reducing the dose of an opioid while maintaining satisfactory analgesia is to combine the opioid with an NSAID. The combination can decrease postoperative pain and opioid requirements by 20% to 50%. NSAIDs, especially those with COX-2 inhibitory activity, have been shown in a number of major epidemiological studies to reduce significantly the risk of several types of cancer, including colon, breast, and prostate cancers. However, those studies were related to the chronic use of NSAIDs. The article by Forget et al.[2] is of particular interest because their results suggest that an NSAID, given as a single dose during surgery, may also significantly reduce cancer recurrence after surgery. They reviewed 319 consecutive patients who had mastectomy for breast cancer during a 4.5-year period. Just more than half (55%) of the patients were given ketorolac IV immediately before skin incision. Cancer recurrence after surgery was lower ($P < 0.001$) in patients given ketorolac (6%) compared with the 17% recurrence in patients who did not receive ketorolac. The authors acknowledge several important limitations of their study. It was retrospective, nonrandom, and patients also received a number of other drugs that could have influenced recurrence, including diclofenac administered postoperatively for pain relief to more than half of the patients. Rather surprisingly, the authors found no association between cancer recurrence and the use of diclofenac, which, similar to ketorolac, is an NSAID with approximately equal activity at COX-1 and COX-2, so it would be expected to have a similar influence on cancer recurrence. Despite these reservations, the analysis of their data is sufficiently robust that the implications of their findings cannot be ignored.

Increased expression of COX-2 occurs in many types of cancers and is a crucial element not only in the pathogenesis and dissemination of tumors but also in increasing their resistance to apoptosis, and with the generation of prostaglandins and related compounds that support carcinogenesis.[16] Blocking overexpression by COX-2–selective NSAIDs can induce apoptosis and tumor regression and inhibits the angiogenesis important for tumor growth and metastasis.[17] In addition to the inhibition of COX-2 and prostaglandin synthesis by NSAIDs, recent studies have suggested that COX-independent pathways may also contribute to the anticancer actions of COX-2–selective NSAIDs.[18,19] This may be an action specific to celecoxib because it inhibited the growth of human prostate cancer cell lines at concentrations comparable with those achieved clinically, whereas rofecoxib had no effect over the same concentration range.[19] Therefore, there are good arguments for using COX-2–specific inhibitors in anesthesia; in addition to providing analgesia thereby reducing the amount of opioids needed for optimal pain relief, they can contribute to minimizing the risk of tumor spread and growth.

Although some cancers progress very rapidly, the majority progress slowly, at least in the early stages. For some patients, malignant cells may have been present in the body for years without any clinical sign of cancer. Indeed, some individuals may never develop overt signs of cancer despite cancer cells being present. This is tumor dormancy, a phenomenon whereby cancer cells persist below the threshold of diagnostic detection for months to decades. Patients who are free of clinically detectable disease for >20 years after treatment may still have circulating tumor cells.[20] Some dormant cancer cells may remain in an asymptomatic, nondetectable, and occult state for the life of the individual.[21] Autopsies of victims of trauma have revealed that most apparently healthy individuals harbor microscopic primary cancers.[22]

Dormant tumors are kept in check by the immune system, but any disruption of this equilibrium can allow them to escape from immune control and proliferate.[23,24] In addition, for a tumor to progress beyond a diameter of 1 to 2 mm requires an "angiogenic switch" characterized by an imbalance between pro- and antiangiogenic factors, allowing the development of angiogenesis. This interrupts the dormant state, triggering invasive tumor growth.[25] The implication is that many, indeed perhaps the majority, of our patients may be harboring a dormant cancer. Any factor that upsets this imbalance, such as surgery and anesthesia, could trigger activation of these cells leading to the development of overt cancer. Unfortunately, at this time, there is no reliable method for detecting the presence of dormant cancer cells.

In conclusion, even though the evidence is inconclusive and at times conflicting, we cannot ignore the possibility that anesthesia may contribute to the recurrence of cancer, months or even years after cancer surgery. Less clear, but equally worrying, is the possibility that anesthesia could activate dormant cancer cells in an individual undergoing noncancer surgery, with the development of an overt cancer that otherwise might never have materialized in the lifetime of that individual. So what should we do? An obvious choice is to use regional anesthesia when feasible, alone or in combination with general anesthesia, to minimize the amount of opioid administered, and to consider using NSAIDs, especially specific COX-2 inhibitors. Of course, what we really need are good prospective, randomized, and controlled clinical trials. These studies will be difficult, requiring large numbers of patients and considerable effort. However, without the results from such studies, we cannot make the informed judgments that will allow us

to offer safe anesthesia to our patients while avoiding the devastating consequences of cancer long after the anesthetic has worn off.

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CME

The Role of the Perioperative Period in Recurrence After Cancer Surgery

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A wealth of basic science data supports the hypothesis that the surgical stress response increases the likelihood of cancer dissemination and metastasis during and after cancer surgery. Anesthetic management of the cancer patient, therefore, could potentially influence long-term outcome. Preclinical data suggest that beneficial approaches might include selection of induction drugs such as propofol, minimizing the use of volatile anesthetics, and coadministration of cyclooxygenase antagonists with systemic opioids. Retrospective clinical trials suggest that the addition of regional anesthesia might decrease recurrence after cancer surgery. Other factors such as blood transfusion, temperature regulation, and statin administration may also affect long-term outcome. (Anesth Analg 2010;110:1636–43)

The idea that surgery promotes local cancer recurrence and distant metastasis is not novel. In fact, >2 millennia ago, observations concerning the negative impact of surgical manipulation on cancer progression were documented. A. Cornelius Celsus, author of "De Medicina," who established the first staging system of cancer, believed that only *cacoethes* (the first stage of cancer) should be removed, because other stages would be irritated by the treatment.[1] Likewise, Alfred A.L.M. Velpeau (1795–1867) noticed that surgical removal of cancer was associated with the return of the disease and that the operation tended to accelerate tumor growth.[1] Modern therapies such as chemotherapy and radiation have eliminated many cancer fatalities. Nevertheless, despite our advances in cancer treatment technique, metastatic recurrence still remains the leading cause of death from cancer.

Several theories have been advocated to explain the frequent incidence of cancer recurrence, most notably residual minimal disease,[2] dissemination of tumor cells at the time of surgery,[3,4] and possibly tumor dormancy[5] (a period when cancer cells are quiescent before progressive growth). Also, surgery creates profound metabolic, neuroendocrine, inflammatory, and immunological stress.[6–9] This surgical stress response includes the release of chemical mediators that have been directly and indirectly implicated in cancer growth. These mediators could cause an upregulation of major promalignant pathways, resulting in a disruption of normal tumor homeostasis, thus promoting local and distant metastasis. Importantly, the type of anesthesia may play a role in this process and could indirectly promote malignant cell development. In this article, we briefly review possible mechanisms involved in the effect of surgery on cancer recurrence and then discuss how anesthetic management could potentially influence these mechanisms, thereby affecting long-term patient outcome.

IMMUNITY AND CANCER

The idea that the immune system recognizes cancerous cells as "nonself" and thereby destroys them was first established by Paul Ehrlich a century ago and was fostered by Burnet and Thomas under the immunosurveillance hypothesis.[10] They suggested that the immune system could actually eliminate cancer cells before they are clinically detectable. It was clear, however, that the immune system is unable to destroy cancer cells completely, as evidenced by the persistence of tumor despite a competent immune system. Subsequently, the concept of immunoediting was born.[10] Under this theory, the immune system is believed to "inadvertently" promote tumor progression by clearing some tumor cells and thereby selecting for those cells most resistant to immune system clearance.

The process of immunoediting is divided into 3 steps. The first step represents the "elimination phase" where cells of the innate and adaptive immune system recognize and destroy tumor cells. The second step is the "equilibrium phase" where it is postulated that the immune system keeps cancer cells in check for a variable period of time. The third step is called "escape" whereby tumor cells evade immunity and become overt tumors.[10] The mechanisms underlying these events are not entirely understood and include alteration in antigen presentation, secretion of immunosuppressive agents, and stimulation of inhibitory pathways. Thus, the immunosuppressant effects of surgery through the secretion of proinflammatory and antiinflammatory cytokines could shape the journey of residual minimal disease toward immune evasion and growth. This hypothesis remains without definitive support at this time.

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THE SURGICAL STRESS RESPONSE AND CANCER

Although the primary role of the stress response after surgery is to augment the healing process, either overactivity or underactivity of host-defense mechanisms paradoxically may lead to negative consequences. For instance, the surgical stress response may provide optimal conditions for persistence of residual minimal malignant disease after surgery. Surgery has been suggested to accelerate the development of preexisting micro metastases and to promote the establishment of new metastases.[4,11] It is believed that the postoperative period is the most vulnerable period for potential metastasis after surgery. This vulnerability is mostly attributed to suppression of cell-mediated immunity, the first-line defense mechanism against cancer.[4] The depression of the immune system occurs within hours of surgery, lasts for several days, and is proportional to the extent of surgical trauma.[12] For example, patients with low levels of natural killer (NK) cell activity undergoing primary cancer surgery have been shown to have a higher rate of cancer-related morbidity and mortality. This association has been demonstrated in patients with colorectal,[13,14] gastric,[15] lung,[16] as well as head and neck cancer.[17,18] The underlying mechanisms of postoperative immune suppression have not been completely established; however, existing data strongly suggest a role for the neuroendocrine system, inflammatory system, and the HPA (hypothalamic-pituitary-adrenal) axis.[19]

Role of the Neuroendocrine System

As early as 1919, scientists demonstrated that young students with pulmonary tuberculosis who were exposed to academic stress had reduced phagocytic capacity to eliminate the pathogen.[20] This was an early demonstration of the effect stress has on the immune system. Likewise, stress has long been considered as a contributor to cancer development.[21] Levels of stress biomarkers, primarily epinephrine and norepinephrine, are elevated in the perioperative period.[19] These neurotransmitters are believed to be responsible for the relationship between stress and cancer progression.[22] This is thought to happen via interaction with β_1- and β_2-adrenergic receptors expressed by tumor cells. Catecholamines have been shown to directly increase the invasive potential of ovarian cancer cells via β-adrenergic upregulation of matrix metalloproteinases[23] and activation of STAT-3 (signal transducer of activation and transcription), a contributor to malignant cell proliferation and survival.[24] Catecholamines also have been shown to increase the production of vascular endothelial growth factor in ovarian cancer cells,[25] and to influence the migration of multiple cancer cell lines including breast, ovarian, and colon cancer.[26] Catecholamines have been shown to influence cell migration and angiogenesis via stimulation of β_1 and β_2 receptors[27–29] in addition to suppressing cell-mediated immunity (CMI).[4]

Role of the Inflammatory System

Cancer is often considered an anarchic cell replication process beyond any form of control or recognition; however, this is a profound oversimplification. In fact, cancer growth and metastasis are very complex processes with cell replication merely representing the tip of the iceberg. Within the tumor microenvironment lies a machinery of highly sophisticated malignant cascades where several products of the inflammatory system such as cytokines, chemokines, prostaglandins (PGs), and cyclooxygenase (COX) are believed to promote cancer progression through immunosuppression, resistance to apoptosis, and promotion of angiogenesis.[30] This is true of the role of chronic inflammation for certain forms of cancer, but it is not clear whether acute inflammation, such as occurs in the perioperative period, results in the same outcomes. Nonetheless, Goldfarb and Ben-Eliyahu[2] suggested that an increase in the level of cytokines (interleukins, IL-6 and IL-8), and PGE_2 in combination with a decrease of T helper type 1 cell-induced cytokine production (IL-2, interferon γ), could account for the profound suppression of NK cytotoxic activity in the perioperative period.

Role of the HPA Axis

Pain, a potent stimulant of the HPA axis, has been implicated in causing immunosuppression, making pain management particularly important in the cancer surgery patient. Pain activates the HPA axis and the sympathetic nervous system, thus setting off a cascade of events that leads to immunosuppression. Acute pain has been shown to suppress NK cell activity[31,32] and promote tumor development in animals.[33] Not surprisingly, provision of pain relief has been shown to attenuate surgery-induced increases in metastatic susceptibility in animals.[34]

POSSIBLE TARGETS FOR METASTASIS PREVENTION BY THE ANESTHESIOLOGIST

Given that the surgical stress response seems to increase opportunities for cancer dissemination and metastasis at the exact time that cancer cells may be released into the circulation, is it possible to minimize these detrimental effects by an appropriate choice of anesthetics? The influence of anesthesia on the stress response to surgery has been investigated in depth. Our goal is to review the anesthetic interventions (Table 1) that affect pathways with a link to tumor progression (Fig. 1).

Opioids

Opioids have long been the mainstay of treatment of cancer-related pain and are an important modality for the prevention of perioperative pain. As stated above, pain leads to CMI suppression, and its treatment is therefore particularly important. Unfortunately, it also has been established that opioids (morphine in particular) inhibit cellular and humoral immune function in humans.[35–37] There are no data directly implicating opioids in cancer genesis in humans, but animal data strongly suggest that they may contribute to cancer recurrence in the clinical setting. For example, in rodent studies, it was demonstrated that morphine is proangiogenic and promotes breast tumor growth.[38,39] This tumor-promoting effect of opiates was also demonstrated with fentanyl,[40] although in other studies, synthetic opiates did not seem to exhibit immunosuppressive effects. Instead, fentanyl was shown in healthy volunteers to increase NK activity.[41] Morphine has not been demonstrated to be tumor promoting in all models; e.g., it was found to promote apoptosis and cell

Table 1. Overview of Reported Anesthetic Effects on Tumor Genesis and Recurrence

Surgical stress response and cancer
Stress and surgical excision of the primary tumor can promote tumor metastasis[4,11]
Neuroendocrine system
General anesthesia accompanied by surgical stress may suppress immunity, presumably by directly affecting the immune system or activating the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system[19]
Inflammatory system
Promotion of cancer progression through immunosuppression via cytokines, chemokines, prostaglandins, COX[30]
Pain
Suppression of NK cell activity[31,32] and promotion of tumor development in animals[33]
Opioids
Opioids inhibit cellular and humoral immune function in humans[36]
Morphine inhibits spontaneous and cytokine-enhanced NK cell cytotoxicity[35–37]
In contrast, IV fentanyl increases NK cell cytotoxicity and circulating CD16(+) lymphocytes in humans[41]
Opioid-induced promotion and stimulation of angiogenesis[39]
β-adrenergic blockade
β-blocker (nadolol) and a prostaglandin synthesis inhibitor (indomethacin) attenuated the metastasis-promoting effects of surgery when used alone or in combination[11]
COX inhibitors
COX inhibitors may prevent metastatic progression and attenuate opioid-induced immunosuppression in rats[11]
The combination of COX-2 inhibitor etodolac and β-blocker propranolol can efficiently prevent immunosuppression after surgery[26]
COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumor growth, metastasis, and mortality in a murine breast cancer model[51]
Anesthetic induction agents and volatile anesthetics
Suppression of NK cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane[63]
Regional anesthesia
Studies in animals show that regional anesthesia and optimal postoperative analgesia independently reduce metastasis[8,9]
Retrospective studies in humans support a benefit of regional analgesia for patients undergoing surgery for breast, colon, or prostate cancer with respect to reduction of recurrence[72–74]
Perioperative blood transfusion
Perioperative blood transfusion is associated with poorer outcome for patients with colorectal cancer recurrence[82]
Perioperative hypothermia
Hypothermia leads to a reduction in cell-mediated immunity, particularly NK cells, and an increase in lung tumor retention and metastasis in rats[87]

COX = cyclooxygenase; NK = natural killer; CD16 = cluster of differentiation.

death in an adenocarcinoma model[42] and in Jurkat cells.[43] Inhibitory effects of morphine on tumor growth have been found in human and animal models as well. For example, in a mouse model, the repeated administration of morphine resulted in decreased tumor cell–induced tissue destruction.[44] This observation was verified in a series of clinical studies showing that pre- and postoperative administration of morphine reduced systemic dissemination of tumor cells.[44–46] This potentially protective effect of morphine on tumor growth was attributed to enhanced T cell–mediated immune responses,[47] physiologically active μ opioid receptor splice variant,[48] inhibition of nuclear factor-κB,[49] and nitric oxide release through the constitutive nitric oxide synthase pathway.[50] Evidently, morphine-tumor interaction is complex, its mechanisms are not completely unraveled, and to a certain extent, contradictory. Further studies in this field are essential to elucidate this interaction. The effects of neuraxial administration of morphine on tumor progression have not been extensively studied. As much smaller doses are used for neuraxial administration, it seems likely that any effects of opioids would be less than after systemic administration.

COX Inhibitors

Using a mouse model, Farooqui et al.[51] demonstrated that the chronic use of morphine leads to a stronger expression of COX-2 in tumor cells that increased PG production, which impaired analgesia and increased tumor angiogenesis, growth, metastasis, and mortality.

In addition, they showed that inhibition of COX-2 by administration of celecoxib prevented morphine-induced tumor growth and metastasis and increased survival. This suggests that COX-2 inhibitors may be used in conjunction with opioid to decrease pain in cancer patients, while counterbalancing the negative effects of opioids on immune function. Even in the absence of opiates, COX-2 inhibitors show promise in preventing cancer growth and metastases in animal models. They have multiple effects, including inducing apoptosis,[52–54] decreasing the levels of angiogenic factors,[55–57] and decreasing tumor microvascular density.[26,52]

Indomethacin, a nonselective COX inhibitor, attenuated the metastasis-promoting effect of surgery in rats.[11] Whereas the intraoperative use of indomethacin may be associated with increased blood loss because of COX-1 inhibition, a selective COX-2 inhibitor might be a feasible adjunct that can be used to attenuate perioperative immunosuppression.

In summary, some opiates and COX inhibitors can be used effectively in the cancer surgery patient. The use of celecoxib, a COX-2 inhibitor, is approved by the Food and Drug Administration for the prevention of colorectal cancer in high-risk patients with preexisting susceptibility such as familial adenomatous polyposis. Opioids are probably best used in conjunction with COX inhibitors or when administered via a neuraxial technique. COX inhibitors may prevent metastatic progression and, in addition to their synergistic analgesic properties, attenuate opioid-induced immunosuppression. Although both nonselective COX and selective COX-2 inhibitors are effective, it is recommended that the latter be used to minimize the chance of bleeding and chance of gastric irritation. The risk of cardiovascular complications should additionally be evaluated before their use.

α_2-Adrenoceptor Agonists

Since the 1980s, clonidine, an antihypertensive drug with sedative properties, has been used as an adjuvant to local anesthetics in various regional techniques to extend the duration of the block.[58] Dexmedetomidine is indicated for sedation in patients receiving mechanical ventilation in the intensive care unit. In 2006, Vázquez et al.[59] published the first study to describe the presence of α_2-adrenoceptors in human epithelial breast cell lines. In 2008, Bruzzone et al.[60] demonstrated a significant enhancement of mouse mammary tumor growth induced by clonidine. In that study, incubation for 2 days with the α_2-adrenoceptor agonists

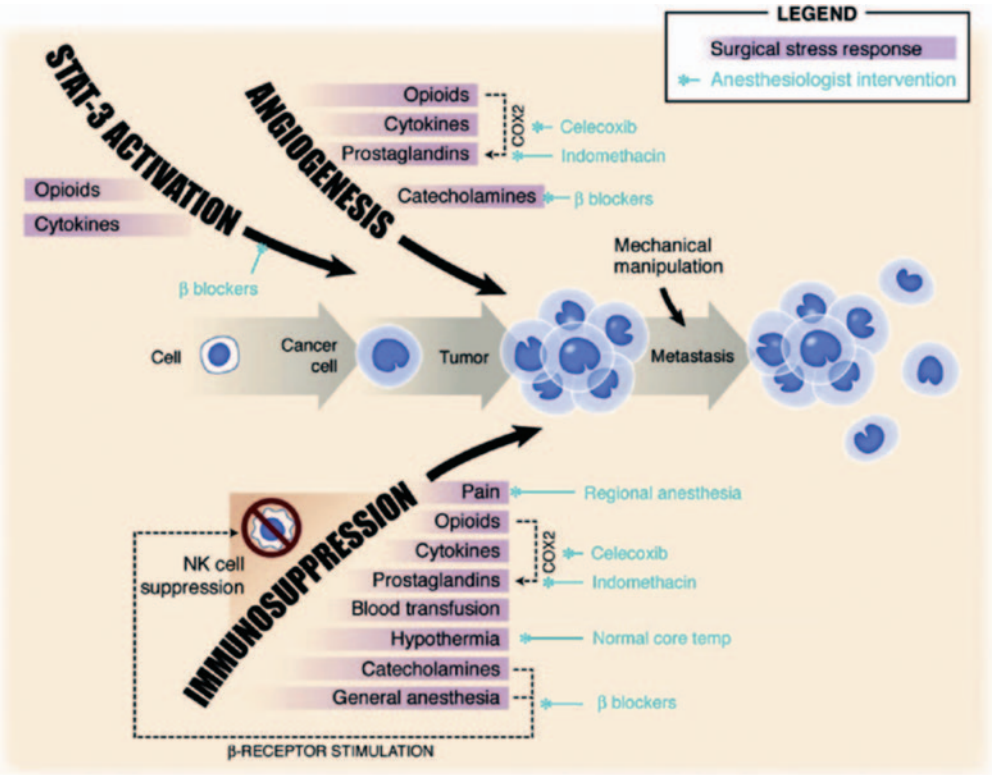

Figure 1. Perioperative mechanism of immunosuppression. STAT = signal transducer of activation and transcription; COX = cyclooxygenase; NK = natural killer.

(clonidine 0.1 $mg \cdot kg^{-1} \cdot d^{-1}$ and dexmedetomidine 0.05 $mg \cdot kg^{-1} \cdot d^{-1}$) significantly enhanced proliferation of the mammary tumor cells. The α_2-adrenoceptor antagonists yohimbine (0.5 $mg \cdot kg^{-1} \cdot d^{-1}$) and rauwolscine (0.5 $mg \cdot kg^{-1} \cdot d^{-1}$) completely reversed the enhancement of tumor growth of clonidine. These results suggest that the α_2-agonist clonidine exerts its enhancement on tumor growth by enhancing cell proliferation and decreasing cell apoptosis, whereas the inverse agonist (i.e., an agent that exerts the opposite pharmacologic effect of an agonist) rauwolscine exerts its protective action both by enhancing apoptosis and reducing cell proliferation. However, the group receiving yohimbine alone showed a nonsignificant but constant increase in tumor growth, whereas rauwolscine alone diminished tumor growth significantly, behaving as a reverse agonist. Therefore, the possibility of blocking this α_2-adrenoceptor–mediated tumor enhancement by hormones released during stress could be an interesting adjuvant therapy for breast cancer patients.[60]

β-Adrenergic Blockade

Hasegawa and Saiki[61] demonstrated a relationship among stress, tumor growth, and β-adrenergic activation independent of glucocorticoid levels in mice. They also showed that the administration of β-blockers abrogated this effect. A combination of β-blockers and COX-2 inhibitors improves immune competence and reduces the risk of tumor metastasis after surgery in animals.[26] Palm et al.[62] demonstrated that use of β-blockers in mice with prostate carcinoma inhibited lumbar lymph node metastases. It seems that β-blockers act by inhibition of catecholamine's induced signal transducer and activator of transcription 3 (STAT-3) activity. STATs are a family of transcription factors that regulate the expression of certain immune system genes. Given the available animal data on the effect of catecholamine on cancer progression and the chemopreventive effect of β-blockers, it seems possible that β-blockers may be beneficial in preventing metastatic progression in humans.

Anesthetic Induction Drugs and Volatile Anesthetics

Melamed et al.[63] demonstrated in rats that ketamine, thiopental, and halothane reduced NK cell activity and increased lung tumor retention and metastasis. The number of circulating NK cells per milliliter of blood was reduced significantly by ketamine and thiopental. The effect of halothane was similar, but did not reach statistical significance.[63] The authors suggested that a reduction in NK cell activity might have a major impact on the resistance to tumor development. The interaction of ketamine with α- and β-adrenoreceptors could be one reason for the suppression of NK activity and the promotion of metastasis.[64] Although the mechanism for immune suppression induced by thiopental or volatile anesthetics remains to be elucidated, it is not related to the anesthetic state per se.[63] Of interest, propofol did not exhibit these effects; instead, propofol seems to have protective effects through various mechanisms, including inhibition of COX-2,[65] inhibition of PGE_2, but also through enhancement of antitumor immunity.[66] Ke et al.[67] showed in patients undergoing open cholecystectomy that the combination of propofol and remifentanil

resulted in an increase in antiinflammatory cytokines IL-10 (known to have antitumor activity and help with healing and repair), as compared with inhaled anesthesia with isoflurane. Inada et al.[68] found in patients undergoing supratentorial tumor excision that propofol anesthesia mitigated the adverse effects of surgical stress-induced immune response better than isoflurane. It would be intuitive therefore to think that total IV anesthesia is preferable to an inhaled technique for patients undergoing cancer surgery.

Although less information is available on other drugs used for anesthesia induction, they may affect the immune system as well. For example, midazolam decreases IL-8 levels. This may contribute to immunosuppression because IL-8 is a chemotactic and activating factor that mediates neutrophil adhesion and margination and is essential for host defense.[69]

Regional Anesthesia

Regional anesthesia, including spinal and epidural anesthesia, reduces the stress response caused by surgery, which is believed to be a mediator of postoperative immunosuppression.[70,71] Regional anesthesia attenuates the surgical stress response by blocking afferent neural transmission. This prevents noxious afferent input from reaching the central nervous system. The addition of regional anesthesia to general anesthesia also results in less overall use of opioids and volatile anesthetics. This association may be beneficial to patients undergoing cancer surgery, because it should theoretically result in less immunosuppression.

In a retrospective analysis of patients undergoing surgical treatment for breast cancer, Exadaktylos et al.[72] demonstrated that the use of paravertebral nerve block in combination with general anesthesia was associated with a longer cancer-free interval and a lower incidence of recurrence. Similar results were shown in other retrospective studies of the use of epidural local anesthetics in prostate cancer and colon cancer surgery.[73,74] Moreover, in a large-scale study in patients with melanoma, substitution of local anesthesia for general anesthesia independently predicted a decrease in tumor recurrence.[75] Also, a recent study of the effect of paravertebral blocks and propofol on cytokine response during breast cancer surgery noted a decrease in tumorigenic cytokines IL-1β/IL-8 and an increase in IL-10, a known antitumor cytokine.[76] The results of these studies should be interpreted cautiously, and there still is no clear evidence whether a simple change in anesthetic practice could affect patient survival. Several multicenter prospective randomized controlled trials are underway, which will test the hypothesis that local or metastatic recurrence after several types of cancer surgery will be decreased in patients randomized to a regional anesthetic technique in comparison to those receiving general anesthesia.[77]

Anemia and Perioperative Blood Transfusion

Anemia is an ominous sign for the cancer patient. Caro et al.[78] conducted a systematic quantitative review and demonstrated that anemia is associated with increased postoperative morbidity and mortality in all forms of cancer, with decreased local control in surgically treated squamous cell carcinoma[79] and decreased survival in non–small cell lung carcinoma.[80] It may seem logical that transfusing the anemic cancer patient would lead to an increase in survival; however, evidence suggests that transfusion poses an independent risk to the cancer patient.

In 1973, Opelz et al.[81] proposed the idea of transfusion-related immunomodulation (TRIM) after recognizing that kidney transplant recipients who received >10 U of allogenic blood had better allograft survival. The demonstration of TRIM has led many to hypothesize that patients undergoing surgery for cancer are at an increased risk for metastatic recurrence if they receive blood products. A recent meta-analysis conducted by Amato and Pescatori[82] suggests this may be correct for patients with colorectal cancer. The authors reviewed 36 studies involving >12,000 patients and found a moderate association between perioperative blood transfusion and colorectal cancer recurrence with an odds ratio of 1.42 (95% confidence interval, 1.20–1.67). These findings call for carefully restricted indications for perioperative transfusions in colorectal cancer patients operated on for cure, and await the results of future studies addressing the role of surgery-related risk factors on the need for transfusion and disease recurrence.[82] However, perioperative transfusion requirement and transfusion within 30 days of operation were not significant predictors of survival for patients with pancreatic ductal adenocarcinoma.[83]

There are >200 published reports on transfusion-related metastatic recurrence with no official consensus. In fact, the only consistency among published data is that cancer patients who receive blood transfusions during surgery tend to do worse. This is independent of whether the blood is allogenic, autogenic, or leukocyte reduced. We are still awaiting human data with regard to the age of the blood products; however, a link between cancer progression and aged erythrocytes was recently demonstrated in a rat model.[84] Nevertheless, it seems that both anemia and blood transfusions are associated with poorer outcomes in cancer patients. Perhaps factors influencing the need for blood transfusion have a greater bearing on prognosis than the receipt of blood itself. For the anesthesiologist, it is important to ensure that the patient is medically optimized before surgery, that all attempts are made to perform minimal blood loss surgery, and that transfusions are used judiciously.

Perioperative Hypothermia

Perioperative hypothermia is associated with an increase in wound infections.[85] In fact, maintaining normothermia is more effective than perioperative antibiotics in the prevention of wound infections.[85] Hypothermia also causes increased blood loss and predisposes patients to blood transfusions.[86] Additionally, hypothermia in combination with surgery and general anesthesia has been shown to lead to a reduction in CMI, particularly NK cells, and an increase in lung tumor retention and metastasis in rats.[87] Although a retrospective analysis could not confirm this finding in humans,[88] it seems important that the anesthesia provider maintains normothermia in cancer patients. This simple measure may lead to a reduction in cancer recurrence after surgery and will most assuredly lead to a reduction in perioperative infections, blood loss, and need for blood transfusion.

Statins

Statins first attracted interest for cancer prevention as an unexpected result of safety monitoring in large randomized controlled trials of statins' and other lipid-decreasing drugs' effectiveness in preventing cardiovascular disease. This monitoring was implemented because the randomized controlled trials showed consistent increases in statin-associated noncardiovascular disease mortality.[89] The safety results, however, indicated that statins did not increase cancer incidence or cancer mortality. In fact, subsequent intensive clinical and observational studies and preclinical data showed significant statin-associated reduction in overall cancer incidence, the most promising of which are colorectal, prostate, breast, and skin cancers.[90,91] This has been further highlighted by 2 large population-based studies that showed statin-associated reduction in the risk of colorectal and advanced prostate cancers.[92]

The effects of statins have been shown to occur through 3-hydroxy-3-methylglutaryl coenzyme A reductase-dependent or -independent pathways such as binding to lymphocyte function associated antigen 1, which has an important role in leukocyte migration and T cell activation.[93] One study of ischemia and cancer indicated that statins augmented blood flow to the ischemic tissue but did not increase blood flow or capillary density in implanted colon tumors. In fact, the growth of these blood vessels was substantially delayed, suggesting an antiangiogenic effect of statins in carcinogenesis.[94] The beneficial effects of statins on carcinogenesis have also been linked to their antiinflammatory and immunomodulatory effects on adhesion, inflammatory mediators, major histocompatibility complex II, T helper 1 and 2 cytokines, and C-reactive protein.[95] Statins also seem to induce apoptosis and inhibit proliferation by regulating several signaling pathways in malignant cells.[96] This pleiotropic aspect of statins indicates the broad impact that these drugs can have on public health, which should be defined by well-designed observational studies of cancer within large prospective cohorts.

CONCLUSIONS

It is much too early to write evidence-based guidelines for the anesthesiologist's role in the prevention of cancer recurrence. At this time, we have very interesting animal data (but do not know if these can be extrapolated to medical practice) and very limited, mostly retrospective, clinical studies. Many questions remain unanswered: How much anesthetic exposure is necessary? Do the type, grade, stage, and location of tumor matter? How can we optimally influence the inflammatory response in the postoperative period? As anesthesiologists, we render care to patients coming to the operating room for diverse and complex cancer operations. By this time, the tumor has already grown, micrometastases already exist, tumor manipulation will cause malignant cells to migrate, and in many patients recurrence will occur after a variable period of time. The possibility that perioperative management may alter the rate or incidence of recurrence is tremendously exciting, but much more research is needed in order for this possibility to be conclusively demonstrated.

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