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INVITED REVIEW ARTICLE

Can anesthetic techniques or drugs affect cancer recurrence in patients undergoing cancer surgery?

Hidetomo Niwa · David J. Rowbotham · David G. Lambert · Donal J. Buggy

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Abstract Despite the development of effective chemotherapy and radiotherapy, surgery remains the mainstay treatment of many cancers, requiring anesthesia. Almost all cancer deaths after primary surgery are attributable to recurrence or metastases. Recently it has been hypothesized that the perioperative anesthetic management of cancer patients could potentially affect the risk of recurrence and metastases, which implies a key role for anesthesiologists in choosing anesthetic agents and techniques that optimize the balance between the metastatic potential of the tumor versus its elimination by antimetastatic immune defenses. This review summarizes available experimental information on the potential effects of common anesthetic agents and techniques on cancer metastases and the conflicting retrospective clinical data on regional anesthesia in various types of cancer. A number of prospective, randomized, multicenter, clinical trials are in progress, and their results are eagerly awaited.

Keywords Anesthetic drugs and techniques · General and regional anesthesia · Cancer recurrence · Metastases

H. Niwa
Department of Anesthesiology, Hirosaki University Graduate School of Medicine, Aomori, Japan

D. J. Rowbotham
Department of Health Sciences, University of Leicester, Division of Anaesthesia, Critical Care and Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW, UK

D. G. Lambert (✉)
Department of Cardiovascular Sciences, University of Leicester, Division of Anaesthesia, Critical Care and Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW, UK
e-mail: DGL3@le.ac.uk

D. J. Buggy
Division of Anaesthesia, Intensive Care and Pain Medicine, Mater Misericordiae University Hospital and National Cancer Screening Service Eccles Unit, Dublin, Ireland

D. J. Buggy
Outcomes Research Consortium, Cleveland Clinic, Cleveland, OH, USA

Introduction: cancer, a major killer

The global burden of cancer is still increasing as a result of the growth of the aging population and in spite of well-developed modern medical treatments including surgery, chemotherapy, and radiotherapy. As a result, cancer is the second most common cause of death in economically developing countries [1]. Lung cancer is the most common form in men, comprising 17 % of new cancer cases and 23 % of total cancer deaths; breast cancer is the leading cause of cancer death in women, accounting for 23 % of the total cancer cases and 14 % of cancer deaths [1]. Until the middle of the twentieth century, most deaths in Japan were caused by infectious disease. However, since the end of World War II, these diseases have rapidly decreased because of the development of modern medical treatment, to be replaced by cancer, heart diseases, and cerebrovascular diseases, largely as a result of population aging and the spread of a Western lifestyle. Based on cancer statistics in Japan (2010) reported by the Foundation for Promotion of Cancer Research, cancer is the most common cause of death since 1981, and the cancer sites with the highest mortality rate in 2009 were lung in both men and women, followed by stomach.

Surgery remains the first-line and essential treatment for cancer patients. However, despite complete resection to microscopically negative margins, cancer deaths after surgery

are common because of metastatic recurrence [2, 3]. During cancer resection, many factors may influence the possibility of metastatic recurrence. These factors include (combinations of) the surgery itself, some anesthetic drugs or techniques, acute pain per se, and opioid analgesia per se [3], implying anesthetic management has the potential to minimize cancer recurrence. The purpose of this article is to review the available experimental and retrospective clinical evidence for the effect of anesthetic drugs and techniques on cancer recurrence and discuss how anesthetic management may potentially influence long-term outcome for cancer patients. The literature in this review was obtained from a search of the PUBMED database from 2000 to 2012. Search terms included the combination of "cancer proliferation," "cancer invasion," "cancer migration," "cancer angiogenesis," "cancer metastasis," or "outcome of cancer patients" for each anesthetic drug such as "propofol" or "regional anesthesia."

Pathogenesis of tumor metastases in the perioperative period

Cancer disease starts with the proliferation of the primary tumor. Initially, nutrients are supplied by diffusion, and later neovascularization occurs as a consequence of angiogenic factors produced by the tumor at the local site, enabling nutrient flow via new capillary vessels arising from host tissue, supporting enhanced proliferation [3]. Tumor cells start to penetrate the surrounding normal tissue, reaching the lymphatic or main blood vessels, and enter the host circulation. Subsequently, cells detached from the primary tumor are transported to distant sites, become trapped in capillary beds of distant organs, extravasate, and grow: this is perhaps the most accepted theory currently of how metastasis is established [4–6].

Although the primary tumor can present with life-threatening signs and symptoms, it uncommonly results directly in the death of the patient. Rather, most cancer morbidity and mortality are attributable to recurrence and metastatic spread to other organs. Minimal residual disease (MRD) is the name given to small numbers of cancer cells that remain in the body after treatment, either by disseminating during surgery or from preexisting micrometastases. These residual cancer cells develop into metastatic recurrence and contribute to death following surgery [3, 4, 7].

The immune response to cancer

Cell-mediated immune response

It is well established that cell-mediated immunity (CMI) can recognize cancerous cells as "non-self" and eliminate them in a fashion similar to that mediating homograft rejection. CMI consists of two types of immune response: the innate immune response and the adaptive immune response. Both work in concert to detect the presence of a developing tumor cell and destroy it before it becomes clinically apparent [8].

The innate immune system is a nonspecific system that combats certain microbial infections and neoplasms without prior sensitization and as such can respond to developing tumor cells immediately [9]; this is therefore a first line of defense against cancer progression. Several cell types including macrophages, natural killer (NK) cells, and dendritic cells comprise this system.

NK cells are a crucial component of the innate immune system because they play a major role in destroying tumor cells. They can recognize major histocompatibility complex (MHC) class 1-deficient tumor cells as "non-self" and kill them spontaneously. Recent animal studies have shown that decreased levels of NK cells are associated with decreased resistance to cancer metastasis and enhanced development of malignancies [10]. Moreover, patients with a low NK cell activity have been reported to have a higher incidence of cancer [3]. In addition, patients with high peripheral blood NK cell activity have significantly longer recurrence-free survival time than those with low NK cell activity [10]. However, a meta-analysis of the effect of anesthetic technique on NK cell function showed no difference [11].

Macrophages are another important component of the innate immune system. They colonize rapidly to a local insult and secrete cytokines that attract NK and dendritic cells [12]. These cells may therefore control the first actions of the innate immune response. However, in most solid tumors, the existence of macrophages known as tumor-associated macrophages (TAMs) promote tumor growth and metastasis [13–15]. Indeed, these cells are associated with poor prognosis in non-small cell lung cancer [14]. Macrophages are polarized into two forms of macrophages (M1 and M2), mirroring the Th1 and Th2 cell classification, so that they can have dual functions in their interaction with neoplastic cells (macrophage balance hypothesis) [15, 16]. In the early phase of tumor progression, M1 macrophages predominate; these elicit antigen-specific adaptive immune responses and show antitumor activity. However, in established cancer, M2 macrophages predominate, exhibiting suppression of adaptive immunity in addition to promotion of angiogenesis and tissue remodeling. As a consequence M2 macrophages promote tumor growth [15].

It is also well recognized that systemic antitumor immunity depends on the adaptive immune system mediated by antigen-specific immune cells [17] such as cytotoxic T lymphocytes (CTLs). Tumor cells carrying certain

foreign molecules with MHC class I on their surfaces are recognized as "non-self" and are destroyed in an antigen-specific manner. In tumor vaccine studies, the number of CTLs in peripheral blood correlated with antitumor activity [17]. Moreover, in recent clinical studies, accumulation of CTLs within the tumor were associated with improved patient survival in epithelial ovarian cancer [18], colorectal cancer [19, 20], and melanoma [21].

Perioperative factors potentially affecting the balance between metastatic potential and elimination by immune defenses (Fig. 1)

Surgery

Surgical resection remains the primary treatment for many forms of cancer, supplemented with chemotherapy, radiotherapy, or endocrine therapy. However, even complete macroscopic surgical excision cannot completely eradicate MRD, which may be defined as the presence of microscopic tumor cells that are clinically undetectable but remain despite optimum surgical technique [2, 3]. Furthermore, the very act of surgery, which is essential for tumor debulking, inadvertently increases the risk of metastases by a number of mechanisms [1]: it releases tumor cells into the circulation [2]; the stress response to surgery depresses CMI, including CTL and NK cell function [3]; and surgery per se also reduces circulating concentrations of tumor-related anti-angiogenic factors (e.g., angiostatin and endostatin), increases concentrations of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), and releases growth factors that promote local and distant growth of malignant tissue [3].

This immunosuppression resulting from a "neuroendocrine response" and "cytokine response" to surgery continues for several days [22], with peak suppression at day 3 [23]. However, adjuvant cytotoxic systemic therapy for eliminating MRD is generally delayed for weeks after surgery because induction of this therapy could lead to more immunosuppression and increase the risk of post-surgical infection [2]. Therefore, it is believed that the postoperative period between 'immediately after surgery' and 'instigation of additional therapeutic treatment' is a possible window of opportunity for MRD to flourish [3, 24]. Thus, the probability of metastatic recurrence after surgery depends on the balance between the metastatic ability of MRD versus the antimetastatic ability of host defenses, which implies that minimizing immunosuppression after surgery could limit metastatic recurrence.

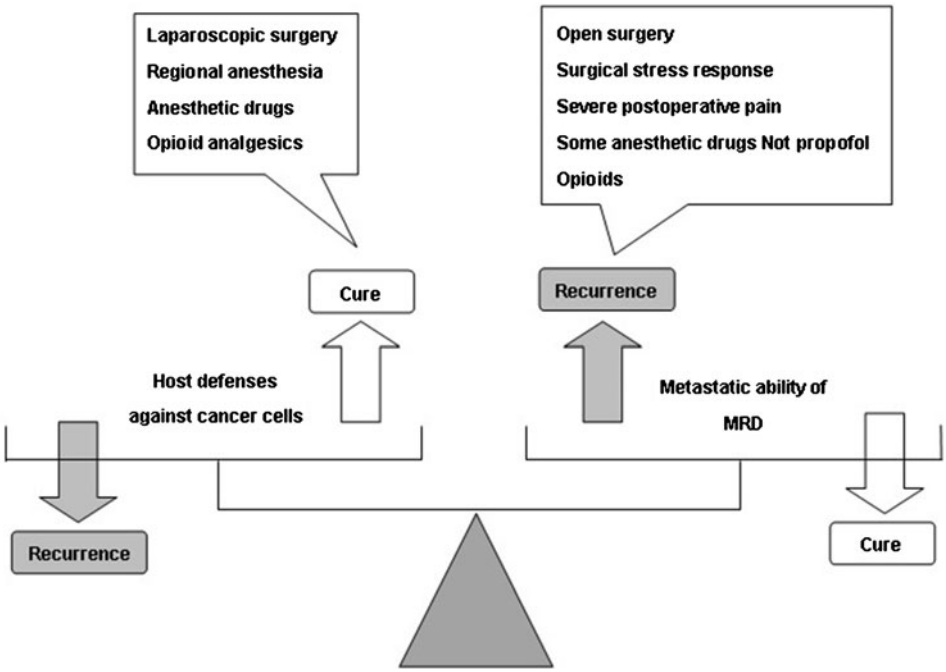

Fig. 1 Balance between the ability of anticancer host defenses and minimal residual disease in the perioperative period. Surgery, most anesthetic drugs, and opioids could inhibit host defenses against malignancy. Regional anesthetic techniques have the potential to decrease the neuroendocrine stress response to surgery, eliminate or reduce the need for general anesthesia, minimize opioid requirements, preserve host defenses, and thereby reduce the risk of recurrence. Current basic data suggest that an appropriate choice of anesthetic drug(s) and opioids has the potential to improve outcome. *MRD* minimal residual disease, defined as the presence of microscopic tumor cells that are clinically undetectable but remain despite optimum surgical technique

Neuroendocrine system

There is evidence that stress response causes neurohormonal and neurotransmitter changes, resulting in cancer development. Swim stress, surgical stress, and social confrontation increased lung metastases in rats implanted with breast cancer cells [25]. Levels of stress biomarkers, primarily catecholamines (epinephrine and norepinephrine), are elevated in the perioperative period, suppressing the CMI system, and potentially resulting in development of cancer disease following surgery [24].

Acute pain

Acute pain, including postoperative pain, suppresses NK cell activity. Improving postoperative pain management has been shown to preserve antitumor NK cell activity after surgery in an animal model [26]. Pain activates the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system, resulting in immunosuppression [24]. Therefore, pain management for cancer patients could affect prognosis. In mice inoculated with B16-BL6 melanoma cells (into the hind paw), tumor growth and lung metastasis were markedly suppressed via relief from cancer pain and surgical stress by administrating morphine as well as by the neurectomy of the sciatic nerve innervating the tumor-inoculated region [27]. Despite this, it is recognized that opioids (the principal analgesics used in perioperative acute pain) could suppress antitumor immunity, as discussed later in this review; however, they also show a favorable immunomodulatory effect in the setting of postoperative pain [3, 28].

Anesthetic drugs

There may also be some potential for anesthetic drugs to directly affect cancer cell biology, including proliferation, invasion, and migration, as well as the CMI system (Table 1). This work emanates largely from cell and tissue culture models, whose applicability to clinical cancer surgery remains unproven and should be considered with caution.

Propofol

Proliferation. Propofol induces apoptosis in HL-60 human leukemia cells via activation of both intrinsic and extrinsic apoptotic pathways, resulting in suppression of tumor growth [29, 30]. It also inhibits growth of EL4 mouse lymphoma cells via the activation of CTLs [30, 31].

Invasion and migration. Propofol inhibits the invasion 'ability' of human cancer cells (Hela, HT1080, HOS, and RPMI-7951) by modulating Rho A, which is a GTPase-modulating integrin [32]. Propofol also decreases the expression of matrix metalloproteinase (MMP)-2 and MMP-9 in the LOVO human colon carcinoma cell line through the suppression of signal-regulated kinase 1 and 2 pathway activation: this is mediated mainly through the

Table 1 Effects of anesthetic agents on cancer progression

Drug	Effect on cancer disease
Propofol	Propofol may directly suppress proliferation [29–31] and invasiveness [32, 33] but not migration [34, 35] of tumor cells. Antimetastatic host defences [36, 38] such as NK cells and cell-mediated immunity are retained, resulting in inhibition or limiting any increase in the development of tumor metastases [32, 36]
Ketamine	Ketamine may directly suppress the proliferation of cancer cells [42] via blockade of NMDA receptors [39–41], but also suppresses host defense against malignancy, leading to development of tumor metastases [36]
Morphine	Strongly suggest suppression of the immune system and increased recurrence and metastasis [3, 24, 28, 68–70], but contradictory effects on angiogenesis [28, 65, 66, 91, 92] and invasion [93, 94].
Fentanyl	Increased NK cell activity [71] leading to inhibitory effects on metastasis at clinically relevant concentrations
Remifentanil	Inhibitory effects on the exaggerated inflammatory response caused by surgery [38, 95, 96], indicating that remifentanil might reduce surgical stress-induced metastasis
Thiopental	Thiopental may reduce NK cell activity, causing increased metastasis [36], but decreased cancer progression including migration and metastasis via downregulation of aquaporins has been reported [52]
Sevoflurane	Sevoflurane may directly suppress the proliferation of cancer cells [53–55], displaying neither decreased antitumor killer activity [57, 61] nor increased metastasis [57]
Isoflurane	Isoflurane has no marked proliferative effects on cancer cells [53] with reduced protection against surgery-induced immunosuppression compared to sevoflurane [61], propofol [38], or remifentanil [38]
Halothane	Anticancer effects might be similar to sevoflurane. Halothane may directly inhibit the growth of cancer cells [53] with decreased [36] or no effect on NK cell activity [74] and no increase in lung metastasis [36, 74]

NK cell natural killer cell, *NMDA receptorN*-methyl-D-aspartate receptor, *PBR* peripheral-type benzodiazepine receptor

γ-aminobutyric acid (GABA)-A receptor, resulting in a decrease in invasiveness [33]. In contrast, Garib et al. [34] reported that propofol increased the number of migrating breast carcinoma cells, as well as the velocity and distance migrated; this occurred via activation of GABA-A receptors secondary to calcium influx via L-type calcium channels and reorganization of the actin cytoskeleton [35].

Interference with the CMI system. Propofol may positively influence the antitumor ability of the CMI system in experimental models. Continuous infusion of propofol into the peritoneal cavity of mice significantly decreased pulmonary metastasis of LM8, murine osteosarcoma cells, with little effect on the growth of the tumor at the inoculation site [32]. Melamed et al. [36] reported that propofol reduced NK cell number but not the activity of circulating NK cells and that there was no increase in lung tumor retention of MADB106, mammary adenocarcinoma cells, in rats. Furthermore, in the clinical setting, propofol anesthesia attenuates surgical stress-induced adverse immune response to a greater extent than isoflurane [37]. In patients undergoing open cholecystectomy, total intravenous anesthesia with propofol and remifentanil (compared to isoflurane) suppressed the stress response to surgery and increased antiinflammatory cytokines (e.g., interleukin-10), which possess antitumor activity [38]. Whole animal cancer models comparing the effect of propofol with other anesthetics need to be performed to further evaluate this potential beneficial effect.

Ketamine

Several in vitro studies have shown that blockade of glutamate receptors suppresses the proliferation of human cancer cell lines [39–41]. In addition, one animal study has shown that NMDA receptor antagonist treatment prolongs the survival of mice with metastatic lung adenocarcinoma and slows the growth of neuroblastoma [39]. These very preliminary data indicate that ketamine might inhibit the proliferation of malignant tumors with an effect on tumor progression. However, Melamed et al. [36] showed that ketamine causes metastases as a result of NK cell suppression in the in vivo rat inoculation model.

Proliferation. Braun et al. [42] reported that ketamine induces apoptosis in human SH-EP neuroblastoma cells.

Benzodiazepines

Benzodiazepines (diazepam and midazolam) activate $GABA_A$ receptors in the central nervous system (producing anxiolysis and sedation) as well as peripheral-type benzodiazepine receptors in immune cells and steroid-producing tissues [43, 44], which are involved in tumor growth. Recent in vitro studies have shown that activating the peripheral-type benzodiazepine receptor (PBR) could suppress cancer growth [44–48]. However, Sakai et al. [43] reported that low concentrations (100–1,000 nM) of diazepam increased the proliferation of Ehrlich tumor cells in vitro and vivo [49]. Consistent with those in vitro results, in an open-label, uncontrolled, multicenter phase II clinical trial of 16 patients with glioblastoma multiforme, recurrence, administration of lonidamine (metabolic inhibitor) and diazepam resulted in 50 % of patients with stable disease over at least 56 days, and treatment periods correlated with time to progression and overall survival [50].

Thiopental

Thiopental is a rapid-onset short-acting anesthetic agent, acting on the $GABA_A$ receptor in the central nervous system, often used for induction. There are few reports on the effect of this agent on the progression of malignancy.

Migration. Recently, aquaporins, which participate in the transport of water and small solutes across the plasma membrane, have been suggested as a therapeutic target for cancer progression [51]. Thiopental induces downregulation of water transport via aquaporins, which could affect cancer migration and metastasis [52].

Interference with CMI system. Thiopental significantly reduced the number and activity of NK cells, increasing MADB106 lung tumor retention [36].

Volatile anesthetics

The volatile anesthetics are still the most frequently used, whether alone or as a part of a balanced anesthesia technique.

Sevoflurane

Proliferation. Sevoflurane inhibited the proliferation of several cancer cell lines such as Caco-2 human colon, Hep-2 human laryngeal cancer, SW620 lymph node metastasis of human colon carcinoma [53, 54], and C6 rat glioma [55], but did not show marked growth alterations in MIA PaCa-2 human pancreatic carcinoma cells [53, 54]. Sevoflurane did not cause cell damage in PC12, rat pheochromocytoma cells [56].

Interference with CMI system. Sevoflurane anesthesia did not attenuate laparotomy-induced immunosuppression in mice, resulting in increased metastasis compared to general anesthesia combined with spinal analgesia. However, in the non-laparotomy group neither an increase in the number of liver metastases nor a decrease in antitumor killer activity in liver mononuclear cells was reported [57].

Isoflurane

Proliferation. Isoflurane did not show marked growth alterations in human cancer cell lines (Caco-2, HEp-2, MIA PaCa-2, and SW620), but inhibited the growth of WI-68, normal fibroblasts, after 6 h exposure [53], and induced apoptosis dose- and time dependently in PC12, rat pheochromocytoma cells, and primary cortical neurons, presumably because of depletion of endoplasmic reticulum calcium stores [56], possibly suggesting a cytotoxic response in noncancer cells. Indeed, isoflurane caused apoptosis and increased production of amyloid beta protein in H4 human neuroglioma cells stably transfected to express human amyloid precursor protein [58, 59].

Interference with CMI system. de Rossi et al. [60] reported antiinflammatory effects of isoflurane in human monocytes, indicating that isoflurane might inhibit the exaggerated inflammatory response caused by surgery. However, during open cholecystectomy, total intravenous anesthesia with propofol and remifentanil suppressed the inflammatory response to surgery to a greater extent than balanced inhalation anesthesia using isoflurane [38]. Furthermore, in laparoscopic pelvic surgery sevoflurane anesthesia produced a lower stress response than that seen with isoflurane anesthesia [61]. Although there is little work on isoflurane, it is not unreasonable to suggest that this agent should not be the first choice of anesthetic for patients undergoing cancer surgery.

Opioid analgesia

Despite the fact that opioids, especially morphine, are often considered the principal treatment against postoperative pain, the majority of experimental reports indicate that opioid administration suppresses both cell-mediated and humoral immune function (although the site is unclear) and facilitates angiogenesis [28, 62].

Morphine

Proliferation. Using cell and animal models, Mathew et al. [63] proposed that activation of the μ opioid receptor was involved in a possible mechanism of Lewis lung carcinoma tumorigenicity. They also showed that the expression of μ opioid receptors was upregulated in lung samples from patients with non-small cell lung cancer and in several human non-small cell lung cancer cell lines. Zagon and McLaughlin [64] showed that morphine-induced apoptosis was small (1–2 %) in various human cancer cell lines. Tumor growth acquires a nutrient supply initially by diffusion, but later requires neovascularization [3]. Therefore, angiogenesis is required for proliferation of tumors. However, at present, it remains unclear how morphine affects angiogenesis when administered to patients despite several studies having been performed. Morphine stimulates endothelial cell proliferation and migration via the transactivation of growth factor receptors [28] mediated by the mitogen-activated protein kinase (MAPK) pathway [65]. Consistent with these reports, Gupta et al. [66] concluded that morphine stimulated human microvascular endothelial cell proliferation and angiogenesis by activating MAPK/extracellular signal-regulated kinase phosphorylation via G_i/G_0-coupled G-protein receptors It also promoted tumor neovascularization in MCF-7 and a human breast cancer xenograft model [66] by increased migration of human breast cancer (MDA-MB-231 and MCF7) [67].

Interference with CMI system. The majority of reports indicate immunosuppressive effects of opioids in experimental studies [3, 24, 28, 68–70]. But the précises site is controversial (immune cell or other). However, the picture of morphine as somehow facilitating cancer metastases is clouded by some studies showing favorable immunomodulation following perioperative morphine administration [28].

Fentanyl

Fentanyl has an analgesic potency about 80 times that of morphine and is also widely used to treat perioperative acute pain and chronic cancer pain.

Interference with CMI system. In seven healthy human volunteers, short-term administration of fentanyl increased NK cell cytotoxicity, but did not affect neutrophil phagocytic function, neutrophil antibody-dependent cell cytotoxicity, percentage of lymphocyte populations, T-lymphocyte proliferative response, or antibody response to a pneumococcal vaccine inoculation [71]. On the other hand, one animal study has shown that high-dose fentanyl (0.1–0.3 mg/kg) suppresses NK cell cytotoxicity and induces a dose-dependent increase in lung retention of MADB106 rat breast cancer cells in rats [72].

Regional anesthesia

There is growing speculation that anesthetic techniques could affect long-term outcome in cancer patients by preserving host defense against malignancy (Fig. 2). Theoretically, regional anesthesia attenuates a number of perioperative risk factors for metastases because it decreases the neuroendocrine stress response to surgical tissue injury as well as the surgical stress-induced increase in proinflammatory cytokines, relieves perioperative acute pain, eliminates or reduces the need for general anesthesia, and minimizes opioid requirement [73]. Until prospective human trials designed to investigate the effect of anesthetic technique on cancer outcome have been published, no

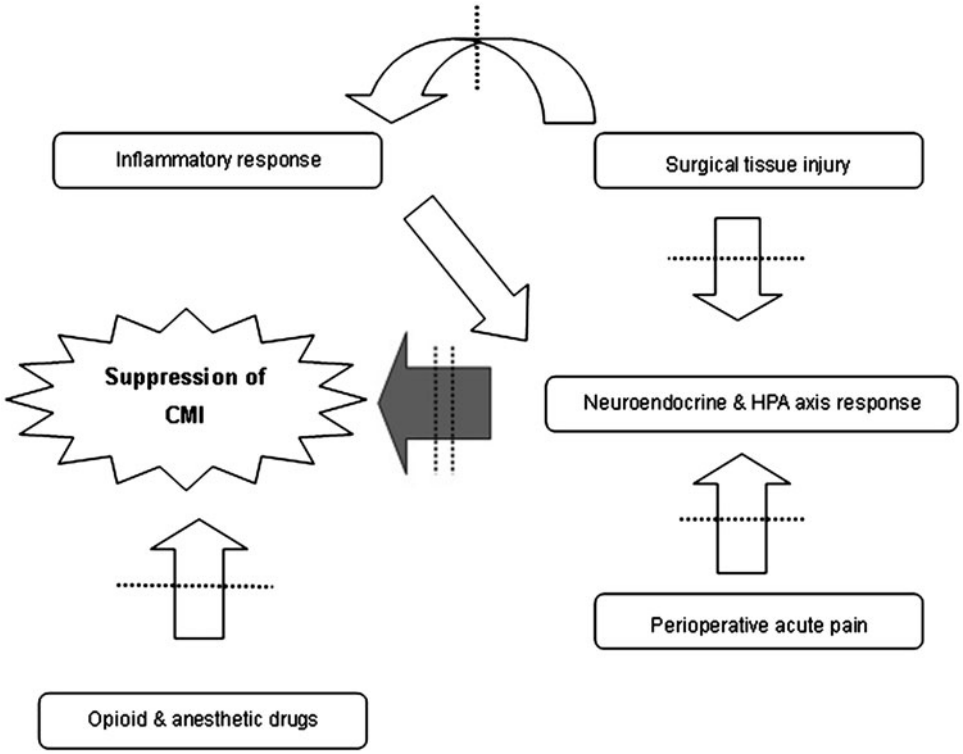

Fig. 2 Potential benefits of regional anesthesia. Perioperative risk factors for cancer recurrence lead to the suppression of host defense against cancer progression. Regional anesthesia decreases the neuroendocrine stress response to surgical tissue injury as well as the surgical stress-induced increase of proinflammatory cytokines, relieves perioperative acute pain, eliminates or reduces the need for general anesthesia, and minimizes opioid requirements. *CMI* cell-mediated immunity, *HPA axis* hypothalamic–pituitary–adrenal axis

change in clinical practice is indicated. Some transitional research around this issue is moderately supportive of the hypothesis. Addition of spinal block to general anesthesia attenuates surgery-induced metastatic development in rats inoculated with MADB106, adenocarcinoma cells [74], as well as in mice inoculated with liver metastatic EL4 cells [57] by preserving the host defense against cancer. In another in vitro study, serum from patients receiving propofol combined with paravertebral anesthesia for breast cancer surgery decreased proliferation, but not migration, of cultured estrogen receptor-negative human breast cancer MDA-MB-213 cells compared with that from patients receiving sevoflurane and opioid anesthesia [75].

Retrospective clinical studies

Almost every conceivable cancer type amenable to primary resection has been the subject of a retrospective analysis evaluating anesthetic technique. The results are conflicting, with almost equal numbers indicating or denying a possible association between anesthetic technique and cancer outcome. In retrospective studies of patients undergoing breast [76], colon [77, 78], rectal [79], and prostate [80, 81] cancer surgery, regional anesthesia such as paravertebral nerve block [76] and epidural anesthesia [77–79] was associated with a decrease in recurrence or metastases [76, 78, 80, 81] as well as an enhanced survival among patients without metastases [77, 79]. On the other hand, in a retrospective analysis of 99 men who had radical prostatectomy, no difference was observed between general anesthesia and combined general/epidural anesthesia for disease-free survival [82]. Furthermore, no effect of anesthetic technique on overall survival was detected in patients undergoing percutaneous radiofrequency ablation of small hepatocellular carcinoma when comparing epidural with general anesthesia [83]. An analysis of more than 42,000 patients who underwent colectomy for colon cancer found that epidural use was associated with improved 5-year overall survival, but not actual cancer recurrence, compared with patients who received general anesthesia and opioid analgesia. The reason for these findings is unclear [84].

A retrospective analysis of colorectal cancer patients who had laparoscopic surgery found no effect of epidural or spinal analgesia compared with systemic opioid analgesia [85], while on the other hand retrospective analysis of 275 malignant melanoma patients suggested a beneficial association with spinal regional anesthesia compared with general anesthesia [86].

Prospective clinical studies

As already mentioned, the results of retrospective studies are contradictory, but only prospective randomized, controlled trials can confirm a causal link between anesthetic technique and cancer recurrence. Some small, translational studies are supportive. In 32 women undergoing primary

surgery of breast cancer, propofol/paravertebral anesthesia with postoperative paravertebral analgesia showed decreased IL-1β, MMP-3, and MMP-9, and a significant increase in IL-10, compared to sevoflurane/morphine anesthesia with postoperative morphine analgesia [87]. In another trial of 35 patients undergoing major surgery for colon cancer, general anesthesia combined with epidural analgesia showed increased levels of antiinflammatory cytokines such as IL-4 and IL-10 compared with general anesthesia alone [88]. This antiinflammatory influence of regional anesthesia may support a beneficial effect on host immune resistance to malignancy. Moreover, in a randomized controlled clinical study, intraoperative use of epidural anesthesia was associated with an increased recurrence-free time after surgery in ovarian cancer patients ($n = 182$) [89]. However, despite encouraging results of some studies, a long-term follow-up study by Myles et al. [90] of a previous prospective randomized trial evaluating other outcomes found that use of epidural block in major abdominal surgery was not associated with improved cancer-free survival.

Ongoing and future work

The Outcomes Research Consortium (Cleveland Clinic, Cleveland, OH, USA) among others, is supporting some randomized controlled trials initiated in Dublin, Ireland evaluating regional anesthesia and other anesthetic and analgesic techniques on long-term cancer outcome, the results of which are eagerly awaited [3].

Summary

There is growing interest in the potential effect of perioperative factors during cancer surgery on longer-term recurrence or metastases. This is, as yet, unsupported by level 1 or 2 evidence because results from ongoing prospective clinical trials are still a number of years away. It is certainly premature to write evidence-based guidelines for anesthetic use. This is a growing area of research and one that will benefit from a close collaboration between laboratory and clinical scientists.

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