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REVIEW

Perioperative care and cancer recurrence: Is there a connection?

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Abstract

Cancer is the second most common cause of death in the United States. Metastatic disease is a more important cause of cancer-related death relative to primary tumor progression. Surgical excision is the primary treatment for most malignant tumors. However, surgery itself can inhibit important host defenses and promote the development of metastases. An altered balance between the metastatic potential of the tumor and the anti-metastatic host defenses, including cell-mediated immunity and natural killer cell function, is a plausible mechanism of increased cancer metastasis. This article reviews the increasingly recognized concept of anesthetic technique along with perioperative factors and their potential to affect long-term outcome after cancer surgery. The potential effect of intravenous anesthetics, volatile agents, local anesthetic drugs, opiates, and non-steroidal anti-inflammatory drugs are reviewed along with recent literature and ongoing clinical trials in this area. Regional anesthesia is increasingly emerging as a safer option with less cancer recurrence potential as compared to general anesthesia. Blood transfusion, pain, stress, use of beta-blockers, and hypothermia are other potentially important perioperative factors to consider.

Key words: Cancer; Recurrence; Survival; Anesthesia; Perioperative; Factors

Core tip: Cancer mortality is frequently related to metastatic disease. An altered balance between the tendency of the tumor to spread *via* metastasis and the body's anti defense processes is the most plausible mechanism of cancer spread. This comprehensive review summarizes the role of anesthetic technique and perioperative interventions and their influence in cancer recurrence. An exhaustive compilation of the latest research and ongoing clinical trials in this area is presented to the reader.

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INTRODUCTION

Cancer is a major source of morbidity and mortality throughout the world. Recent statistics from the Centers for Disease Control indicate that cancer is the second most common cause of death in the United States[1]. Although age-adjusted death rates for cancer and heart

disease have slowly declined since 1991, approximately one in four deaths are still attributed to cancer. It is estimated that in the United States alone, there were over 1.6 million new cancer diagnoses in 2012 and over 577000 deaths from cancer[2]. Of those cases, the most common cancer diagnoses are prostate in men (29%) and breast in women (29%), followed by lung cancer (14% in men and women), and colorectal cancer (9% in men and women). However, lung cancer remains the most common cause of cancer-related mortality in both men and women[2].

Of the deaths due to cancer each year, only about 10% are due to complications of the primary tumor[3]. The vast majority of cancer-related deaths occur due to metastatic disease. Local recurrence and metastasis rates are influenced by a multitude of factors. For example, one study of nearly 3000 women with Stage Ⅰ, Ⅱ, or Ⅲ, breast cancer from 1985 to 2001 who underwent surgery followed by chemo- or hormonal therapy found an overall recurrence rate of 11% at 5 years and 20% at 10 years[4]. However, recurrence rates at 5 years were nearly 50% lower in the subgroup that had Stage Ⅰ breast cancer (7%) than those with Stage Ⅲ breast cancer (13%) at diagnosis. Additionally, risk of recurrence differed substantially between those with hormone receptor positive versus negative tumors. Overall recurrence rates of breast cancer would likely be lower today, as treatment advances have been made since the time of this study, including the introduction of aromatase inhibitors and trastuzumab immunotherapy. However, this study illustrates that cancer recurrence is multifactorial, and even for a specific type of cancer can vary substantially based upon stage and grade at diagnosis, biologic characteristics of the tumor, initial treatment modalities, and host immune function.

Surgical excision is considered the first line of treatment for most solid organ tumors. However, even "curative" surgery leaves the possibility of microscopic residual disease[3]. Tumor cells can be left at the excisional margins or released into circulation during the dissection and removal of the bulk tumor mass. It is also possible that primary tumor cells intravasate preoperatively and travel to distant organs, forming undetected micrometastases that continue to grow postoperatively[5-7]. In addition, surgery and perioperative factors such as pain stimulate neuroendocrine and stress responses that suppress cell-mediated immunity (CMI) and promote tumor growth and metastasis[5,7].

Metastases occur *via* a complex process of cellular changes and mutations balanced against host immune defenses. Primary tumors initially receive blood and nutrients from simple diffusion. As the tumor grows, it develops mutations in factors such as vascular endothelial growth factor (VEGF), which promote angiogenesis[3,8]. Eventually, some tumor cells acquire mutations that allow invasion through the basement membrane into blood vessels and lymphatic channels, where they can be transported throughout the body. In patients with intact immune systems, most tumor cells are destroyed in circulation[3]. However, surviving cells have potential to extravasate through capillary beds in distant organs, proliferate, and form micrometastases. Each primary tumor requires a particular biologic microenvironment to survive[9]. Therefore, micrometastases tend to flourish in certain organs and not others. For example, prostate cancer typically metastasizes to the bone and colon cancer to the liver[3].

The host cellular immune system is a critical defense mechanism against the development of metastases[10]. Early on, cancer cells have weak antigenicity. With time, random mutations accumulate and the cells become more antigenic[3]. Natural killer (NK) cells and cytotoxic T cells appear to be key players in immune surveillance[11,12]. NK cells, which are activated by interleukin-2 (IL-2) and interferon-γ (IFN-γ), are able to spontaneously recognize and lyse tumor cells, as well as activate other immune cells[3,13]. Loss of Major Histocompatibility Complex class I (MHC- Ⅰ), which is almost universally expressed on normal cells, is a common mechanism for tumor cells to evade T-cell recognition. However, NK cells are able to recognize this abnormality and trigger apoptosis of the neoplastic cells[13]. There is evidence from human studies that patients with depressed NK cell function have a higher incidence of cancer and of metastatic disease after "curative" surgery[14-17]. There is also evidence that increased stress, like that occurring in the perioperative period, causes a reduction in NK cell activity[17]. In animal models, decreased NK cell activity due to stress has been associated with increased tumor development[18]. For all of these reasons, immunotherapies designed to enhance NK cell function are currently an area of extensive research for cancer treatments[13].

The essential nature of immune surveillance in preventing the development of metastatic lesions is also seen in solid-organ transplant recipients. These patients, who are on life-long immunosuppressive therapy, have a significantly increased risk of developing metastases[19]. Based upon the current evidence, identifying and targeting factors in the perioperative period that influence the immune system, and particularly NK cell function, could have a significant impact on development of metastases and long-term survival in cancer patients.

RATIONALE FOR REGIONAL ANESTHESIA

The curative treatment of cancer usually involves surgical resection of the primary tumor and/or metastases. Although complete eradication of the malignancy is the primary goal, the immune suppression associated with surgical stress may lead to tumor extension[20]. On the other hand, with the marked decrease of anesthesia-related morbidity and mortality in the last decades and the difficulty in discriminating differences between anesthetic techniques, it has been suggested that new analyses on long-term anesthetic effects should focus on patient-centered outcomes, including but not limited to cancer recurrence[21].

Effects of surgery and anesthesia on tumor cells

There is a large amount of data from anecdotal reports, observational and retrospective human studies and animal studies that emphasizes the so-called "deleterious" effects of general anesthesia and or surgical stress on cancer recurrence and outcomes. The authors would like to fore warn the reader that in the absence of large randomized prospective studies the clinician should not immediately change practices based on this data.

The immune response to cancer plays a pivotal role in recovery from oncologic disease. Cancer is characterized by the presence of genetic abnormalities that lead to alterations of regulatory processes[22]. As a result, the malignant cells express different surface antigens that, coupled with MHC class I molecules, are presented to the immune system and recognized by CD8 T cells, leading to cytotoxic antineoplastic responses and immunomodulatory counterbalancing responses[23,24]. The role of cytokines such as IFN-γ is essential to prevent primary tumor development and growth[25,26]. Besides the activity of adaptive immunity (T and B cell-receptor mediated), NK cells, derived from innate lymphoid cells, constitute a primary line of defense against tumor cells by both direct cytotoxicity and IFN-γ production[27,28]. Evidently the immune system is unable to completely clear cancer cells in some instances. Moreover, in a process called immunoediting, tumor cell growth is actually promoted by the immune system[29]. The immunosuppresive effect of surgery and anesthesia depends on a fine balance between activation/inhibition of pro-inflammatory and anti-inflammatory pathways.

Effects of surgery: During the last few years, it has been recognized that even though surgery is the mainstay for cancer treatment in many patients, surgical intervention may accelerate tumor progression and micrometastasis development[10,30,31]. Right after surgical removal of the primary tumor, an array of local and systemic consequences ensues. First, due to mechanical manipulation of the tumor, malignant cells can get access to blood vessels and lymphatics[32-34]. In addition, important humoral factors related to angiogenesis and cell proliferation, such as VEGF, are released from the primary source of cancerous cells during surgery[35-37]. Conversely, with tumor removal, local production of antiangiogenic factors such as angiostatin and endostatin[38,39] is markedly reduced. Taken together, the combination of the aforementioned factors creates a favorable *milieu* for neoplastic cell proliferation and metastasis development.

CMI is assumed to be important to control residual tumor activity once the primary tumor is resected; however, because of a variety of mechanisms, many perioperative factors tend to suppress CMI. Stress associated with surgery activates the sympathetic nervous system and neurohumoral pathways, resulting in high concentration of mediators that affect CMI at different levels.

The stress response includes the massive release of multiple mediators including glucocorticoids, endogenous opioids, catecholamines, angiogenic factors, and cytokines. Special interest has been focused on the role of catecholamines and prostaglandins and their secondary effect on other mediator production. Tissue concentration of cyclooxygenase-2 (COX-2), an enzyme necessary for prostaglandin E2 synthesis, is low under normal circumstances[40]; however, in malignant tumors, its production is abnormally high[41]. Inhibition of COX-2 activity has been shown to decrease neoplastic invasive potential and tumor angiogenesis in animals and humans[42,43]. On the other hand, some clinical studies have shown an inhibitory effect of β-adrenergic blockade on stress induced tumor progression[44], whereas *in vitro* studies have evidenced the ability of β-adrenergic agonists to stimulate malignant cell proliferation even in absence of stress[45,46]. Several mechanisms have been implicated in adrenergic enhancement of disease progression, including IL-6 and IL-8 overproduction by both the immune system and the tumor, apoptosis resistance[44,47-50], suppression of NK cell cytotoxic activity[51], angiogenic stimulation[52], increased tissue invasion and increased arachidonic acid signaling[53-55].

Acute pain: Studies in animals have shown that acute pain inhibits NK cell activity[56-58] and tumor progression[59,60], whereas other experiments have demonstrated enhanced NK cytotoxicity and increased lymphocyte proliferation[61]. On the other hand, treatment of postoperative pain with opioids has been able to reduce cancer recurrence, despite their potential "prometastatic" effect[62] (see opioid section below). It is difficult to ascertain the independent effect of acute postoperative pain on tumor progression, as it overlaps with the bimodal effect of opioids. It is likely that the stimulating effect of opioids on tumor cells is only evident in the absence of acute pain[63]. Finally, there are no studies evaluating the impact of chronic pain on cancer recurrence.

Volatile anesthetics: The association between volatile anesthetics and cancer progression was observed more than four decades ago. Lundy *et al*[64] proposed that the combination of halothane, surgery and immunosuppression increased pulmonary metastases in mice inoculated with tumor cells. Shapiro *et al*[65] found that lung tumor progression was accelerated in mouse models when exposed to halothane and nitrous oxide. There are no human studies on the isolated effect of volatile anesthetics on tumor spread and metastasis, due probably to the multifactorial nature of immune system and tumor cell biology during the perioperative period. However, since inhaled anesthetics have direct and indirect effects on different aspects of the immune response, it could be hypothesized that they are important factors in postoperative immunosuppression and residual malignant cell invasion and migration.

Extensive experimental work has been carried out to elucidate the mechanisms underlying the immunosuppression induced by volatile anesthetics. Immunomodulatory

properties have been attributed to these agents[66], including their effect on neutrophil function; reactive oxygen species production; and macrophage, lymphocyte and NK cell physiology[67]. As neutrophils are a primary line of host defense, it is speculated that as halothane, isoflurane, and sevoflurane are able to blunt either neutrophil adhesion to endothelium *via* intercellular adhesion molecule-1 (ICAM-1), and superoxide production *in vitro*[68-71], early phases of immunity might be compromised.

The role of the interaction between inhaled anesthetics and Hypoxia Inducible Factors (HIF) has received special attention in the last few years[72]. These transcription factors are involved in organ protection in hypoxic situations[73-75]. Isoflurane, desflurane and xenon have been shown to stimulate the expression of HIF in pharmacologic preconditioning, analogous to the one occurring under hypoxic conditions[76-79]. There is an association between high levels of HIF and clinical prognosis in cancer, colorectal and breast cancer. It is speculated then that tumor cells could also benefit from pharmacologic preconditioning induced by volatile agents.

The effect of volatile anesthetics on neutrophils and HIF, as mentioned above, tends to favor tumor progression *via* pharmacologic preconditioning and depression of primary immunity. However, the depressant effect of these agents on the immune system might turn out to be beneficial in some instances. For example, sevoflurane and desflurane have been shown to reduce invasion of colorectal cancer cells through down-regulation of matrix metalloproteinases[80].

In regard to lymphocyte function, sevoflurane and isoflurane are able to interfere with integrin-mediated lymphocyte adhesion by means of an allosteric block[81,82]. In addition, volatile agents are able to induce caspase-dependent apoptosis in T-lymphocytes[83]. These qualitative abnormalities added to lymphocytopenia induced by agents such as halothane and nitrous oxide, lead to depression of CMI and potential tumor progression in the perioperative period[84].

Since NK cells represent a key element in the immune response against malignant cell progression and growth, many studies have focused on the effect of inhaled agents on this cell line[85]. *In vitro* studies have shown that halothane and enflurane reversibly depress NK cell cytotoxicity elicited by IFN[86,87]. The underlying mechanism for this effect is poorly understood but might be related to cortisol-mediated inhibition[88] or CD8 T lymphocyte stimulation[89].

Finally, although most studies linking volatile anesthesia to cancer progression show the immune system as the target for their facilitating actions on tumor cells, recent evidence shows oxidative DNA damage induced by isoflurane in elective surgery[90]. Furthermore, Musak *et al*[91] showed that healthcare personnel exposed to volatile anesthetics exhibit higher frequency of chromosomal damage. These findings open a window for possible direct carcinogenic effects of inhaled anesthetic agents, making the issue of perioperative tumor progression an even more complex matter.

Intravenous anesthetics: Intravenous (IV) anesthetics are used to induce hypnosis during anesthesia. As is the case for volatile anesthetics, special interest in IV agents has developed in the last decades in relation to neoplastic tissue growth and propagation in the perioperative period. Propofol, a non-barbiturate induction agent used in anesthesia and critical care (and its lipid carrier vehicle) has anti-inflammatory properties by a direct effect on innate immunity[92]; however, it appears to lack effect on NK cell and lymphocyte function[93]. Furthermore, the Th1/Th2 ratio was increased by propofol[94]. Th1 cytokines activate CMI whereas Th2 cytokines stimulate B cells. Also relevant to antineoplastic immune response, is the fact that propofol impairs monocyte and macrophage function, including phagocytosis and cytokine production[95-97], in addition to its ability to induce apoptosis in these cellular groups[97].

Etomidate is a hypnotic agent used in cases where hemodynamic stability is a concern. It has the ability to suppress cortisol production; however, there are no reports linking this effect to tumor progression. Peripheral-type benzodiazepine receptors and gamma aminobutyric acid (GABA) are expressed in breast cancer cells[98]. Since both receptors are targeted by etomidate, Garib studied the effect of the anesthetic agent in breast cancer cell migration *in vitro*, finding that it has no significant effect[99]. Ketamine is a dissociative anesthetic agent, widely used in cancer with analgesic purposes. Ketamine significantly decreases NK cell cytotoxicity[93,100], but at lower preincisional doses has shown to control pain with minimal effect on NK-cell in oral maxilofacial surgery[101].

Opioids: Opioid derivatives are widely used in anesthesia and pain management. There is growing evidence suggesting a role of these medications in cancer progression and metastasis. The effect of opioids on tumor progression could be related to their ability to interfere with the barrier integrity against tumor propagation[102], the angiogenic potential of the tumor, a direct immunosuppressive effect, or a combination of factors[103].

Although the mechanisms underlying opioid-induced immunosuppression are not yet fully understood, it is recognized that μ-receptors[104] and neuroendocrine mechanisms may play a role[105-107]. The activation of opioid receptors elicits the stimulation of adrenocorticotropic hormone production with its consequent cortisol release, which suppresses immune responses[108,109]. Natural and synthetic opioids are potent activators of the sympathetic nervous system to produce high concentrations of catecholamines[110], which are involved in tumor progression (see above).

Fentanyl has a dose-dependent depressant effect on T lymphocyte function and NK cell cytotoxicity that parallels lung tumor progression in animals. Remifentanil has not been widely studied in reference to its effects on malignancies, however there is a single study evaluating its effect on neutrophil function, showing that neither fentanyl nor remifentanil suppress neutrophil respiratory burst *in vitro*[111]. Tramadol limits NK cell suppression

caused by surgery in rats[112,113] and preserves immune function in cancer patients[114]. There is a lack of evidence linking alfentanil, hydromorphone, and oxycodone to cancer metastasis.

Morphine is the opioid most widely studied in association to cancer recurrence. Peripheral opioid receptors are involved in modulation of cell proliferation[115] and apoptosis[116]. *In vitro* studies have shown the pro-apoptotic action of morphine on cancer cells by different mechanisms including inhibition of NFκB *via* nitric oxide[117,118], whereas other studies have shown inhibition of apoptotic processes *via* p53[119-121], a key factor in programmed cell death. In general, most studies report the ability of morphine to inhibit tumor cell proliferation *in vitro*[122-124].

Although the immunosuppressive effect of opioids has been widely documented, some reports describe opioids' immunomodulatory properties that might prove beneficial in the context of malignant disease[125-127]. It is reasonable to conclude that the effects of opioids on the cancer immunity depend on the extent of their analgesic action, counterbalancing their primary protumoral effect.

An additional potential confounder here would be psychological symptoms such as depression and its linkages with cancer pain and that those patients with depression are usually on a higher dose of opioids to treat this cancer pain. Cancer chemotherapy in more metastatic and advanced tumors (and those that potentially cause more pain and depression and need more opioids) with pharmacological agents that induce immunosuppression has depression as one of its side effects as well[128]. Specifically, IFN-α has been seen to decrease serum activity of prolyl endopeptidase (PEP). This enzyme is a cytosolic peptidase that is widely distributed in human tissues and body fluids. By playing an important role in intracellular protein turnover PEP is indirectly involved in the pathophysiology of psychiatric dysfunction in relation to mood disorder. High-risk melanoma patients receiving IFN-α were seen to have a clear decrease in PEP activity in the first four weeks of therapy[129]. Van Gool *et al*[130] also investigated the levels of PEP in patients with metastatic renal cell carcinoma receiving immunotherapy and concluded that a role for PEP in the pathophysiology of IFN-α induced mood disturbance can neither be confirmed nor excluded.

The complex interplay of opioids, cancer pain, immunotherapy, depression and immunomodulation means that clearly the effect of opioids themselves on cancer recurrence and metastases cannot be clearly elucidated and there is much more associated with this cause and effect relationship than what is plainly evident based on current literature.

Local anesthetics: Amide-type but not ester-type local anesthetics possess anti-inflammatory properties[131]. In addition, local anesthetics have antimicrobial properties[132]. Taken together, these effects of local anesthetics have led some to hypothesize that they may have a potential role to deter tumor progression after surgery. Some *in vitro* studies have tested the ability of ropivacaine[133], lidocaine[134], and procaine[135]. Both lidocaine and ropivacaine inhibit TNF-α driven *Src* activation and ICAM-1 phosphorylation in lung cancer tumor cells *in vitro* through a sodium-channel-blockade independent mechanism[136]. Procaine has DNA-demethylating properties[135] that potentiate antineoplastic action of cis-platin[137,138]. There are no clinical studies evaluating the isolated effect of local anesthetics on cancer recurrence and metastases, so that the contribution of the direct effect of these agents to the beneficial effect of regional anesthesia in cancer patients is for now speculative.

Regional anesthesia effects: In vitro and experimental data in animals

The association between pain and immunosuppression has been documented for a long time in animals. Intermittent footshock in rats elicits immune dysfunction including NK cell hypoactivity[57,58,139,140]. On the other hand, Page *et al*[141] demonstrated that postoperative pain is directly involved in surgery-related tumor progression. After these findings, different authors have documented beneficial effects of regional anesthetic techniques on immune function. Wada *et al*[142] demonstrated the preservation of the cytokine balance between TH1 and TH2 lymphocytes as the factor involved on attenuation of liver metastasis by combined regional and general anesthesia in mice. Bar-Yosef *et al*[59] used a rat model to show that spinal anesthesia preserved NK cell cytotoxicity and attenuated metastasis progression after inoculation of adenocarcinoma cells. Finally, Deegan *et al*[143] demonstrated that serum from patients with breast cancer who underwent general anesthesia with paravertebral block inhibited proliferation but not migration of malignant ER-MDA-MB-231 cells *in vitro*.

Regional anesthesia effects: Observational studies

Evidence regarding the facilitation of tumor progression induced by surgery and enhanced by some general anesthetics, has led researchers to postulate that regional anesthetic techniques might ameliorate those deleterious pro-metastatic effects, which could translate into better overall survival rates and recurrence-free survival in cancer patients. One landmark study that opened the window to explore the field of the effect of regional anesthesia on cancer progression was published by Exadaktylos *et al*[144] in 2006. They retrospectively studied 129 patients with breast cancer who underwent mastectomy with axillary clearance, with a follow-up time of 32 ± 5 mo. This cohort retrospective study showed that recurrence and metastasis-free survival was 94% (95%CI: 87%-100%) and 82% (95%CI: 74%-91%) at 24 mo and 94% (95%CI: 87%-100%) and 77% (95%CI: 68%-87%) at 36 mo in the paravertebral and general anesthesia patients respectively (P = 0.012). The study has limitations inherent to its retrospective nature, including selection bias and biological plausibility[145]. With the sample size in a retrospective study like the one of Exadaktylos, it is possible that the association is the result of uneven distribution of risk factors between the groups. For instance,

it is likely that the severity of disease had been the cause of the anesthetic technique decision rather than the consequence. Additionally, the author used the Nottingham Prognostic Score to determine propensity to cancer recurrence, when this scale has not been validated for that purpose[146]. Despite its limitations, this study stands as a landmark publication because it generated the hypothesis of a true association between anesthetic technique and cancer progression, which has led to development of other observational and new experimental studies on the subject.

In 2008, Biki *et al*[147] addressed the issue of the effect of epidural anesthesia/analgesia on cancer recurrence after radical prostatectomy. This retrospective review showed that the epidural plus general anesthesia group had a 57% (95%CI: 17%-78%) lower risk of recurrence compared with the general anesthesia plus opioid group. Limitations of the study that could limit its validity include incomplete information about the protocol used[148]. There is no mention of the quantitative postoperative opioid requirement, which might prove important as there is a relationship between opioids and immune depression/cell proliferation. In addition, no power analysis was performed and there are no data about the number of individuals who had surgery and were not included in the review as well as the number of patients dropped because of inadequate information. The evidence provided by Biki is not enough to change practice; nonetheless, it remains as an important study as it encouraged other authors to design prospective studies to clarify the cause-effect relationship between anesthetic technique and cancer recurrence. A potential pathophysiological mechanism to explain the results of Biki could be the higher Th1/Th2 lymphocyte ratio with regional anesthesia compared with general anesthesia[149]. In contrast to the study of Biki, in 2013 Wuethrich *et al*[150] published a retrospective study of 148 patients with prostate cancer, concluding that general anesthesia combined with epidural analgesia did not reduce the risk of cancer progression or improve survival after radical prostatectomy after 14 years of observation. The main strength of this study was the prolonged follow-up time. However, as no differences were detected, the study might be underpowered. As in any retrospective study, selection bias cannot be excluded. Finally, the general anesthesia group included ketorolac in the analgesic regimen. It has been shown that ketorolac, by its action on the enzyme COX-2, may suppress cancer relapse[151]. It is possible that this effect could have influenced the results. By the same token, Tsui *et al*[152] performed a secondary analysis on 99 patients undergoing radical prostatectomy, who had participated in a previous randomized controlled trial evaluating pain control, blood loss, and transfusion. They found no difference between epidural and control groups in terms of disease free survival after a follow-up time of 4.5 years. Among the 99 patients, 22 were lost to follow-up. Biochemical recurrence was detected in 31% of epidural patients compared to 40% of general anesthesia patients, with a hazard ratio of 1.3 slightly favoring general anesthesia, but with a 95%CI of 0.6-2.7. Despite randomization, the fact that the study was originally designed for different endpoints, renders the study underpowered for evaluating cancer recurrence[153]. Again, the authors call for design of larger prospective trials.

Cummings *et al*[154] in 2012 conducted a retrospective cohort study with 42151 patients who underwent surgery for colon cancer. The results are ambiguous, showing that the patients in the epidural group had a 5-year survival of 61% compared to 55% in the non-epidural group, whereas no significant reduction in cancer recurrence in the epidural group could be demonstrated. In spite of the limitations of a retrospective study including, selection bias despite propensity score use and information bias related to the administrative claims source for procedures; this large population-based study is robust enough to suggest a beneficial effect of epidural anesthesia/analgesia on survival after resection of nonmetastatic colon cancer, although no effect of epidural anesthesia/analgesia on cancer recurrence could be demonstrated. In a retrospective analysis, by means of a multiple regression analysis, Gupta *et al*[155] showed a higher risk of death associated with patient-controlled analgesia (PCA) but not with epidural analgesia in rectal but not colon cancer surgery. This study included 655 patients in Sweden. The inherent limitations of a retrospective study were addressed by the authors; however there might be bias related to group allocation. There is a marked difference in group size (epidural group n = 562, PCA group n = 93), with no apparent cause, which raises the possibility of selection bias. Some confounding variables such as use of steroids and fluid therapy used were not addressed. Finally, the authors stated that the cause of death in both group was not validated. Taken together, the validity of the results from the study by Gupta *et al*[155] is questionable. The results of Christopherson *et al*[156], in a retrospective analysis, also demonstrated a survival benefit of epidural analgesia on survival at 1.46 years in non-metastatic colon cancer surgery. Conversely, Gottschalk *et al*[157] did not find an association between epidural analgesia and cancer recurrence after colorectal surgery; however, a post-hoc analysis suggested some benefit in older patients. This is also a retrospective study that included 509 patients with colorectal cancer. The epidural group had more patients with rectal cancer, higher histologic grade, more adjuvant therapy and fluid loss. Additionally, there is no clear definition of rectal cancer recurrence, and the use of non-steroidal antiinflammatory medications was not adequately reported. These limitations make the results of Forget *et al*[158] inconclusive.

Merquiol *et al*[159] in 2013 published a retrospective study with propensity-based matching of patients with laryngeal and hypopharyngeal cancer surgery under general anesthesia with morphine or cervical epidural analgesia. The epidural group exhibited higher 5-year cancer-free survival (68%; 95%CI: 57%-82%) compared to the non-epidural group (37%; 95%CI: 25%-54%), and increased overall survival. Despite the use of propensity scores, selection bias and influence of confounding factors cannot

be ruled out; nevertheless, this study suggested a possible beneficial effect of neuraxial analgesia in neck cancer. Schlagenhauff *et al*[160] conducted a retrospective analysis of cancer registry data using matched pair analysis investigating survival after malignant melanoma. They found that patients who experienced local anesthesia had higher 10-year survival rates. This effect was visible after 3 years.

Conflicting reports in ovarian cancer have been published recently. Lacassie *et al*[161] found no benefit in overall surival or time to recurrence in patients with advanced stages of ovarian cancer with epidural analgesia/anesthesia. They retrospectively studied 89 patients with propensity score matching and weighting. Again, the limitations of retrospective studies are observed with this study and the exclusion of 9 patients due to incomplete documentation might affect the validity of the results. Binczak *et al*[162] failed to demonstrate a statistically significant association between the perioperative analgesia and recurrence-free survival after abdominal surgery for cancer. This study is a retrospective analysis of patients randomized for a prospective study with different endpoints, and as such is underpowered to detect a difference between analgesic regimens in terms of cancer recurrence and survival. Finally, in a meta-analysis of retrospective and prospective studies on the effect of anesthetic technique on survival in cancer, Chen *et al*[163] suggest that, especially in colorectal cancer, epidural anesthesia and/or analgesia might be associated with improved overall survival in cancer undergoing surgery; however, their results do not support an association between epidural anesthesia and cancer control.

In conclusion, the possible association between regional anesthesia and cancer survival and recurrence, yet intriguing, has emerged mainly from experimental animal studies and retrospective human analysis. Prospective studies, ideally randomized clinical trials are needed to establish causation.

CLINICAL TRIALS OF THE EFFECT OF ANESTHESIA ON CANCER RECURRENCE

It is challenging to design a study with sufficient power and robustness to clearly prove the idea that a specific type of anesthesia can reduce the occurrence of cancer, as long-term follow-up is required. Anesthetic effects must be clearly discernible from a multitude of other factors related to the neoplasm propagation. Interindividual variability in immune system performance as well response to anesthesia further complicates the issue. This also means that large studies are needed to understand the difficult-to-single-out effects of anesthesia on tumor propagation.

The review of clinical trials should be started from animal studies. Bar-Yosef *et al*[59] conducted an interesting study in which rats were subjected to a laparotomy during general halothane anesthesia alone or combined with either systemic morphine or spinal block using bupivacaine with morphine. Control groups were either anesthetized or undisturbed. The animals were subjected to a standard load of adenocarcinoma cells, and the "clinical outcome" was measured by change in tumor load and activity of NK cells. Strikingly, spinal anesthesia significantly reduced tumor load that was initially elevated after surgery. More specifically, laparotomy conducted during general anesthesia alone increased lung tumor retention up to 17-fold. The addition of spinal block reduced this effect by 70%. The number of metastases increased from 16.7 ± 10.5 (mean ± SD) in the control group to 37.2 ± 24.4 after surgery and was reduced to 10.5 ± 4.7 during spinal block. This study is seminal and many follow-up clinical trials used the results generated by Bar-Yosef *et al*[59] to calculate power of their randomized clinical trials even though they did not use any clinical metrics of tumor progression. Further support to this study was brought by Wade *et al*[142]. This group inoculated mice with liver tumor cells *via* laparotomy while the mice were under general anesthesia alone or combined with spinal block. They concurred that spinal anesthesia significantly reduces tumor load. However, both studies are problematic because injecting the cells into the bloodstream and measuring the tumor load later may have little clinical relevance to human patients.

Currently, there is not a finished randomized clinical trial investigating the relationship between type of anesthesia and neoplastic growth. Some studies were terminated without enrolling patients while several other studies are underway but have not yet reported the results.

Study NCT00418457 will investigate the relationship between the addition of regional anesthesia to the general surgery regimen and recurrence of breast cancer. This study is planning to enroll 1100 patients and to investigate the effect of a paravertebral block. Using data from animal experiments, investigators predict such a sample size over 5 years will provide 85% power for detecting a 30% treatment effect at an alpha of 0.05 with a total of four potential stopping points[59,142]. Follow-up is planned for 10 years.

Exadaktylos *et al*[144] have previously shown that the use of regional anesthesia in cancer surgery reduced the risk of recurrence and metastases of breast cancer by four fold. In a recent analysis of a previously conducted study of paravertebral blocks for breast cancer surgery, oppfeldt and carlson evaluated the effects of regional anesthesia on cancer recurrence[164]. Eighty-eight patients having breast cancer surgery were enrolled in this study. The patients received 4-6 paravertebral injections from level C7 through T5 on the side of surgery. The treatment group received a total of 30 mL of ropivacaine 0.5% and the placebo group received placebo injections of isotonic saline in an equivalent volume. Both groups had a standardized anesthesia consisting of propofol, fentanyl and ventilation *via* a laryngeal mask.

Six years or more after surgery the investigators found that local or metastatic recurrence of the cancer in five patients (13%) in the ropivacaine group and in fourteen (37%) patients in the saline group, RR = 0.35 (95%CI: 0.14-0.87). In addition, the mortality related to

the breast cancer was significantly lower in the ropivacaine group (ropivacaine 4, saline 12), RR = 0.32 (95%CI: 0.11-0.92). Also, patients without recurrence of cancer consumed significantly lesser opioids (45 mg morphine equipotent doses) compared to patients with recurrence of cancer (58 mg morphine equipotent doses), $P = 0.016$. The authors concluded that attenuation of surgical stress and reduced opioid consumption reduces the risk of developing metastases[164].

A very similar design is being tested in NCT00684229. In this multicenter clinical trial a comparison of colorectal cancer recurrence will be measured between patients randomly assigned to epidural anesthesia combined with general versus general anesthesia only. Follow-up is planned for 5 years.

In NCT01588847 the investigators hypothesize that patients suffering from malignant melanoma who undergo radical inguinal lymph node dissection will demonstrate less immune function compromise and superior long-term survival when spinal anesthesia is used, compared to general anesthesia. The time frame for this study is 5 years. Investigators will be evaluating in the short term some aspects of immune system performance.

NCT01179308 is focusing on patients undergoing lung resection. Again, investigators propose to evaluate the effect of combined epidural-general anesthesia compared to general anesthesia on cancer recurrence semi-annually over a period of 5 years.

The National Science Council of Taiwan will co-sponsor a study looking into the effect of local infiltration anesthesia with lidocaine and bupivacaine on the recurrence of breast cancer while patients are rendered unconscious with propofol (NCT015332233). A second avenue of this study involves standard general inhalational anesthesia with opioids. Estimated enrollment is scheduled for 40, which seems to be too small to achieve significant power. This number of enrollment is in clear contrast to other the target number of other studies.

The EPICOL study (NCT01318161) enrolls patients after undergoing surgery for colorectal cancer in Sweden. Regional anesthesia in the form of epidural anesthesia will be contrasted to oral narcotics. The follow-up is planned for total of 7 years and the enrollment goal is 400 patients. Additionally, authors of the study plan to conduct large-scale measurements of cytokine and angiogenesis factors in the patient population. No effect of epidural or spinal blockade will be examined. Researchers plan to enroll 60 subjects and measure only immune system functions in the short-term after surgery.

Similarly, NCT01902849 focuses on the modulation of immune aspects after surgery. The investigators will analyze IL-6 and IL-10 levels until 24 h post-op.

In the interesting spin CTC study (NCT01716065), researchers will look at the circulating tumor load in subjects undergoing surgery for primary nonmetastatic cancer. Though this study parallels aforementioned studies in animals, the target goal is 20 subjects.

These clinical trials and the planned studies going forward if properly powered and statistically robust will go a long way in answering the as yet unanswered question of modifying the anesthetic plan to provide a better cancer related outcome for the patient in question.

OTHER POTENTIALLY IMPORTANT FACTORS

Blood transfusion

It is now a well know theoretical fact that transfusion-associated immunomodulation (TRIM) is the driving force behind allogeneic blood transfusion related tumor recurrence. This is related to the immunosuppressive effects of the allogeneic blood[165,166].

Patients undergoing surgery for colorectal cancer have experienced a significant decline in immune function as measured by a reduction in T-helper and NK cell lines. The roles of these cells in the immunopathology of cell defense and tumor immunity have been highlighted in the earlier text[167-170].

So what really is the biggest villain within a unit of allogeneic blood transfusion itself? Much needs to done to reach a precise answer. The current evidence points towards white blood cells[169]. A study investigating patients undergoing resection of gastric cancer randomized patients to allogeneic or autologous transfusion. IFN-γ, T-helper cell, and T-helper/cytotoxic T-cell ratio were reduced in both groups after operation. The reduction was greater in the allogeneic transfusion group. Five days after the operation, levels had returned to baseline for patients receiving autologous transfusions but remained suppressed in the allogeneic group[171]. Literature has not clearly supported TRIM as an effector of cancer recurrence. As might be expected, several potential confounders such as severity or stage of the cancer, and or co-morbid conditions, have emerged and are difficult to control for while designing studies[172]. Other observational studies (esophageal cancer) and randomized control trials (colorectal cancer) have not reported leukocyte depletion or allogeneic white blood cells to affect cancer outcome[173-176]. The clinical evidence of whether TRIM is associated with a worse oncologic outcome, and of whether leukodepletion reduces TRIM, remains unanswered.

Immunotherapy

Opioids have been known to suppress immune response, specifically NK cell activity. It has been seen that in rats that pretreatment with an IFN inducer increases NK cell activity to above baseline in rats and attenuates the fentanyl-induced suppression to above baseline levels[177].

Similarly, when IFN-α and IFN-β are used before surgery in rats, they may offset some of the inhibition of NK cell cytotoxicity associated with surgery and anesthesia[178]. Going forward the use of immunotherapy for cancer in humans during the perioperative period has been proposed, though present literature has not reported significant success[179].

Beta-blockers

A large body of recent data supports the use of beta-blockers in cancer patients. The proposed mechanisms

revolve around the attenuation of the anxiety driven intense sympathetic drive and related IL release during the initial phase of cancer seeding. The growing evidence that norepinephrine and epinephrine affect some types of cancer backs this. The body's "fight or flight" response related to psychological stressors may release these hormones and affect cancer by interacting with molecular pathways already implicated in abnormal cellular replication, such as the P38/MAPK pathway, or *via* oxidative stress. Various studies have shown less distant metastases in patients with prostate[180] and lung cancer[181]. The strongest evidence probably comes from the breast cancer subgroup wherein there is a favorable benefit for cancer recurrence in particular[182,183]. An important consideration with these studies is that all of them are retrospective in nature. Stronger evidence with blinded randomized trials is probably needed before we can think of specifically initiating beta-blockers in the perioperative period to decrease cancer recurrence.

Hypothermia

Based on the premise that hypothermia excites a stress response and glucocorticoid release that in turn increases immunosuppressive effects, hypothermia has a mechanistic linkage to cancer recurrence. In animal studies, a temperature of 30.8 ℃ has been shown to suppress NK cell activity and also suppress resistance to metastasis using a specific tumor model[184]. In humans, mild hypothermia to 35.5 ℃ exacerbates the immunosuppressive effects of abdominal surgery[185].

Stress response

In humans as well as in animals, stress responses have been linked to NK cell suppression, perioperative immunosuppression and increase tumor retention[17,186].

The stress level in cancer patients is associated with the degree of postoperative immunosuppression and has been shown to predict NK cell toxicity and T-cell responses. This may be the reason for success with beta blocker therapy as highlighted in the section above and an area of interest for anesthesiologists.

Future directions

Though much has been said and done about anesthetic technique and cancer recurrence, the question very much remains unanswered. Multiple high quality, well-designed and validated studies are needed before a strong statement can be made one way or the other about the influence of an anesthetic technique on the recurrence and behavior of certain cancer types. The currently available data do favor regional anesthesia as a sole vehicle or in combination with general anesthesia, in addition to an increasing trend to autologous blood transfusion and attenuation of stress responses in the perioperative period. Areas of future interest could be related to some of the other anti-inflammatory and immunomodulatory drugs that we use in the perioperative period. These include a better categorization of various types of opioids, NSAIDs and other analgesics. A greater focus needs to be on longer follow-up of patients in these observational studies and long term outcomes related to the anesthetic technique and perioperative interventions.

As an anesthesiologist and a perioperative physician these variables are important and while we wait for better clinical studies in humans, we have to move to shaping these perioperative factors for better outcomes in surgical cancer patients.

REFERENCES

1 **Hoyert D**, Jiaquan X. Deaths: Preliminary Data for 2011. In: CDC, ed. Atlanta: CDC, 2012: 1-51
2 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087 DOI: 10.3322/caac.21166]
3 **Weinberg R**. The Biology of Cancer. In: Garland Science TFGL, editor The Biology of Cancer. New York, 2007: 587-653
4 **Brewster AM**, Hortobagyi GN, Broglio KR, Kau SW, Santa-Maria CA, Arun B, Buzdar AU, Booser DJ, Valero V, Bondy M, Esteva FJ. Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst* 2008; **100**: 1179-1183 [PMID: 18695137 DOI: 10.1093/jnci/djn233]
5 **Coffey JC**, Wang JH, Smith MJ, Bouchier-Hayes D, Cotter TG, Redmond HP. Excisional surgery for cancer cure: therapy at a cost. *Lancet Oncol* 2003; **4**: 760-768 [PMID: 14662433]
6 **Ceelen WP**, Morris S, Paraskeva P, Pattyn P. Surgical trauma, minimal residual disease and locoregional cancer recurrence. *Cancer Treat Res* 2007; **134**: 51-69 [PMID: 17633047]
7 **Tai LH**, de Souza CT, Bélanger S, Ly L, Alkayyal AA, Zhang J, Rintoul JL, Ananth AA, Lam T, Breitbach CJ, Falls TJ, Kirn DH, Bell JC, Makrigiannis AP, Auer RA. Preventing postoperative metastatic disease by inhibiting surgery-induced dysfunction in natural killer cells. *Cancer Res* 2013; **73**: 97-107 [PMID: 23090117 DOI: 10.1158/0008-5472.CAN-12-1993]
8 **Fidler IJ**. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. *Nat Rev Cancer* 2003; **3**: 453-458 [PMID: 12778135 DOI: 10.1038/nrc1098]
9 **Langley RR**, Fidler IJ. Tumor cell-organ microenvironment interactions in the pathogenesis of cancer metastasis. *Endocr Rev* 2007; **28**: 297-321 [PMID: 17409287 DOI: 10.1210/er.2006-0027]
10 **Shakhar G**, Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: could they reduce recurrence rates in oncological patients? *Ann Surg Oncol* 2003; **10**: 972-992 [PMID: 14527919]
11 **Brittenden J**, Heys SD, Ross J, Eremin O. Natural killer cells and cancer. *Cancer* 1996; **77**: 1226-1243 [PMID: 8608497]
12 **Uchida A**, Kariya Y, Okamoto N, Sugie K, Fujimoto T, Yagita M. Prediction of postoperative clinical course by autologous tumor-killing activity in lung cancer patients. *J Natl Cancer Inst* 1990; **82**: 1697-1701 [PMID: 2231757]
13 **Campbell KS**, Hasegawa J. Natural killer cell biology: an update and future directions. *J Allergy Clin Immunol* 2013; **132**: 536-544 [PMID: 23906377 DOI: 10.1016/j.jaci.2013.07.006]
14 **Orange JS**. Human natural killer cell deficiencies. *Curr Opin Allergy Clin Immunol* 2006; **6**: 399-409 [PMID: 17088643 DOI: 10.1097/ACI.0b013e3280106b65]
15 **Liljefors M**, Nilsson B, Hjelm Skog AL, Ragnhammar P, Mellstedt H, Frödin JE. Natural killer (NK) cell function is a strong prognostic factor in colorectal carcinoma patients treated with the monoclonal antibody 17-1A. *Int J Cancer* 2003; **105**: 717-723 [PMID: 12740924 DOI: 10.1002/ijc.11139]
16 **Kondo E**, Koda K, Takiguchi N, Oda K, Seike K, Ishizuka M, Miyazaki M. Preoperative natural killer cell activity as a prognostic factor for distant metastasis following surgery for colon cancer. *Dig Surg* 2003; **20**: 445-451 [PMID: 12900537 DOI: 10.1159/000072714]

17 **Andersen BL**, Farrar WB, Golden-Kreutz D, Kutz LA, MacCallum R, Courtney ME, Glaser R. Stress and immune responses after surgical treatment for regional breast cancer. *J Natl Cancer Inst* 1998; **90**: 30-36 [PMID: 9428780]
18 **Ben-Eliyahu S**, Page GG, Yirmiya R, Shakhar G. Evidence that stress and surgical interventions promote tumor development by suppressing natural killer cell activity. *Int J Cancer* 1999; **80**: 880-888 [PMID: 10074922]
19 **Penn I**. The effect of immunosuppression on pre-existing cancers. *Transplantation* 1993; **55**: 742-747 [PMID: 8475546]
20 **Yeager MP**, Rosenkranz KM. Cancer recurrence after surgery: a role for regional anesthesia? *Reg Anesth Pain Med* 2010; **35**: 483-484 [PMID: 20975458 DOI: 10.1097/AAP.0b013e3181fa11a9]
21 **Liu SS**, Wu CL. The effect of analgesic technique on postoperative patient-reported outcomes including analgesia: a systematic review. *Anesth Analg* 2007; **105**: 789-808 [PMID: 17717242 DOI: 10.1213/01.ane.0000278089.16848.1e]
22 **Tian T**, Olson S, Whitacre JM, Harding A. The origins of cancer robustness and evolvability. *Integr Biol* (Camb) 2011; **3**: 17-30 [PMID: 20944865 DOI: 10.1039/c0ib00046a]
23 **Chen DS**, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013; **39**: 1-10 [PMID: 23890059 DOI: 10.1016/j.immuni.2013.07.012]
24 **Boon T**, Cerottini JC, Van den Eynde B, van der Bruggen P, Van Pel A. Tumor antigens recognized by T lymphocytes. *Annu Rev Immunol* 1994; **12**: 337-365 [PMID: 8011285 DOI: 10.1146/annurev.iy.12.040194.002005]
25 **Kaplan DH**, Shankaran V, Dighe AS, Stockert E, Aguet M, Old LJ, Schreiber RD. Demonstration of an interferon gamma-dependent tumor surveillance system in immunocompetent mice. *Proc Natl Acad Sci USA* 1998; **95**: 7556-7561 [PMID: 9636188]
26 **Shankaran V**, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature* 2001; **410**: 1107-1111 [PMID: 11323675 DOI: 10.1038/35074122]
27 **Vivier E**, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, Yokoyama WM, Ugolini S. Innate or adaptive immunity? The example of natural killer cells. *Science* 2011; **331**: 44-49 [PMID: 21212348 DOI: 10.1126/science.1198687]
28 **Vivier E**, Ugolini S, Blaise D, Chabannon C, Brossay L. Targeting natural killer cells and natural killer T cells in cancer. *Nat Rev Immunol* 2012; **12**: 239-252 [PMID: 22437937 DOI: 10.1038/nri3174]
29 **Dunn GP**, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity* 2004; **21**: 137-148 [PMID: 15308095 DOI: 10.1016/j.immuni.2004.07.017]
30 **Baum M**, Demicheli R, Hrushesky W, Retsky M. Does surgery unfavourably perturb the "natural history" of early breast cancer by accelerating the appearance of distant metastases? *Eur J Cancer* 2005; **41**: 508-515 [PMID: 15737554 DOI: 10.1016/j.ejca.2004.09.031]
31 **Ben-Eliyahu S**. The promotion of tumor metastasis by surgery and stress: immunological basis and implications for psychoneuroimmunology. *Brain Behav Immun* 2003; **17** Suppl 1: S27-S36 [PMID: 12615183]
32 **Weitz J**, Herfarth C. Surgical strategies and minimal residual disease detection. *Semin Surg Oncol* 2001; **20**: 329-333 [PMID: 11747275]
33 **Oefelein MG**, Kaul K, Herz B, Blum MD, Holland JM, Keeler TC, Cook WA, Ignatoff JM. Molecular detection of prostate epithelial cells from the surgical field and peripheral circulation during radical prostatectomy. *J Urol* 1996; **155**: 238-242 [PMID: 7490843]
34 **Yamaguchi K**, Takagi Y, Aoki S, Futamura M, Saji S. Significant detection of circulating cancer cells in the blood by reverse transcriptase-polymerase chain reaction during colorectal cancer resection. *Ann Surg* 2000; **232**: 58-65 [PMID: 10862196]
35 **Kim SH**, Choe C, Shin YS, Jeon MJ, Choi SJ, Lee J, Bae GY, Cha HJ, Kim J. Human lung cancer-associated fibroblasts enhance motility of non-small cell lung cancer cells in co-culture. *Anticancer Res* 2013; **33**: 2001-2009 [PMID: 23645749]
36 **Goldfarb Y**, Ben-Eliyahu S. Surgery as a risk factor for breast cancer recurrence and metastasis: mediating mechanisms and clinical prophylactic approaches. *Breast Dis* 2006; **26**: 99-114 [PMID: 17473369]
37 **Ekblad L**, Lindgren G, Persson E, Kjellén E, Wennerberg J. Cell-line-specific stimulation of tumor cell aggressiveness by wound healing factors - a central role for STAT3. *BMC Cancer* 2013; **13**: 33 [PMID: 23351302 DOI: 10.1186/1471-2407-13-33]
38 **Szarvas T**, Jäger T, Laszlo V, Kramer G, Klingler HC, vom Dorp F, Romics I, Ergün S, Rübben H. Circulating angiostatin, bFGF, and Tie2/TEK levels and their prognostic impact in bladder cancer. *Urology* 2012; **80**: 737.e13-737.e18 [PMID: 22607948 DOI: 10.1016/j.urology.2012.03.023]
39 **Fukuda H**, Mochizuki S, Abe H, Okano HJ, Hara-Miyauchi C, Okano H, Yamaguchi N, Nakayama M, D'Armiento J, Okada Y. Host-derived MMP-13 exhibits a protective role in lung metastasis of melanoma cells by local endostatin production. *Br J Cancer* 2011; **105**: 1615-1624 [PMID: 22015555 DOI: 10.1038/bjc.2011.431]
40 **Reader J**, Holt D, Fulton A. Prostaglandin E2 EP receptors as therapeutic targets in breast cancer. *Cancer Metastasis Rev* 2011; **30**: 449-463 [PMID: 22002714 DOI: 10.1007/s10555-011-9303-2]
41 **Howe LR**. Inflammation and breast cancer. Cyclooxygenase/prostaglandin signaling and breast cancer. *Breast Cancer Res* 2007; **9**: 210 [PMID: 17640394 DOI: 10.1186/bcr1678]
42 **Condeelis J**, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell* 2006; **124**: 263-266 [PMID: 16439202 DOI: 10.1016/j.cell.2006.01.007]
43 **Wang L**, Chen W, Xie X, He Y, Bai X. Celecoxib inhibits tumor growth and angiogenesis in an orthotopic implantation tumor model of human colon cancer. *Exp Oncol* 2008; **30**: 42-51 [PMID: 18438340]
44 **Sloan EK**, Priceman SJ, Cox BF, Yu S, Pimentel MA, Tangkanangnukul V, Arevalo JM, Morizono K, Karanikolas BD, Wu L, Sood AK, Cole SW. The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res* 2010; **70**: 7042-7052 [PMID: 20823155 DOI: 10.1158/0008-5472.CAN-10-0522]
45 **Palm D**, Lang K, Niggemann B, Drell TL, Masur K, Zaenker KS, Entschladen F. The norepinephrine-driven metastasis development of PC-3 human prostate cancer cells in BALB/c nude mice is inhibited by beta-blockers. *Int J Cancer* 2006; **118**: 2744-2749 [PMID: 16381019 DOI: 10.1002/ijc.21723]
46 **Cole SW**, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. *Clin Cancer Res* 2012; **18**: 1201-1206 [PMID: 22186256 DOI: 10.1158/1078-0432.CCR-11-0641]
47 **Cole SW**, Arevalo JM, Takahashi R, Sloan EK, Lutgendorf SK, Sood AK, Sheridan JF, Seeman TE. Computational identification of gene-social environment interaction at the human IL6 locus. *Proc Natl Acad Sci USA* 2010; **107**: 5681-5686 [PMID: 20176930 DOI: 10.1073/pnas.0911515107]
48 **Shahzad MM**, Arevalo JM, Armaiz-Pena GN, Lu C, Stone RL, Moreno-Smith M, Nishimura M, Lee JW, Jennings NB, Bottsford-Miller J, Vivas-Mejia P, Lutgendorf SK, Lopez-Berestein G, Bar-Eli M, Cole SW, Sood AK. Stress effects on FosB- and interleukin-8 (IL8)-driven ovarian cancer growth and metastasis. *J Biol Chem* 2010; **285**: 35462-35470 [PMID: 20826776 DOI: 10.1074/jbc.M110.109579]
49 **Sastry KS**, Karpova Y, Prokopovich S, Smith AJ, Essau B, Gersappe A, Carson JP, Weber MJ, Register TC, Chen YQ, Penn RB, Kulik G. Epinephrine protects cancer cells from apoptosis via activation of cAMP-dependent protein kinase and BAD phosphorylation. *J Biol Chem* 2007; **282**: 14094-14100 [PMID: 17353197 DOI: 10.1074/jbc.M611370200]
50 **Sood AK**, Armaiz-Pena GN, Halder J, Nick AM, Stone RL,

Hu W, Carroll AR, Spannuth WA, Deavers MT, Allen JK, Han LY, Kamat AA, Shahzad MM, McIntyre BW, Diaz-Montero CM, Jennings NB, Lin YG, Merritt WM, DeGeest K, Vivas-Mejia PE, Lopez-Berestein G, Schaller MD, Cole SW, Lutgendorf SK. Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis. *J Clin Invest* 2010; **120**: 1515-1523 [PMID: 20389021 DOI: 10.1172/JCI40802]

51 **Inbar S**, Neeman E, Avraham R, Benish M, Rosenne E, Ben-Eliyahu S. Do stress responses promote leukemia progression? An animal study suggesting a role for epinephrine and prostaglandin-E2 through reduced NK activity. *PLoS One* 2011; **6**: e19246 [PMID: 21559428 DOI: 10.1371/journal.pone.0019246]

52 **Obeid EI**, Conzen SD. The role of adrenergic signaling in breast cancer biology. *Cancer Biomark* 2013; **13**: 161-169 [PMID: 23912488 DOI: 10.3233/CBM-130347]

53 **Landen CN**, Lin YG, Armaiz Pena GN, Das PD, Arevalo JM, Kamat AA, Han LY, Jennings NB, Spannuth WA, Thaker PH, Lutgendorf SK, Savary CA, Sanguino AM, Lopez-Berestein G, Cole SW, Sood AK. Neuroendocrine modulation of signal transducer and activator of transcription-3 in ovarian cancer. *Cancer Res* 2007; **67**: 10389-10396 [PMID: 17974982 DOI: 10.1158/0008-5472.CAN-07-0858]

54 **Sood AK**, Bhatty R, Kamat AA, Landen CN, Han L, Thaker PH, Li Y, Gershenson DM, Lutgendorf S, Cole SW. Stress hormone-mediated invasion of ovarian cancer cells. *Clin Cancer Res* 2006; **12**: 369-375 [PMID: 16428474 DOI: 10.1158/1078-0432.CCR-05-1698]

55 **Cakir Y**, Plummer HK, Tithof PK, Schuller HM. Beta-adrenergic and arachidonic acid-mediated growth regulation of human breast cancer cell lines. *Int J Oncol* 2002; **21**: 153-157 [PMID: 12063562]

56 **Li Q**, Liang Z, Nakadai A, Kawada T. Effect of electric foot shock and psychological stress on activities of murine splenic natural killer and lymphokine-activated killer cells, cytotoxic T lymphocytes, natural killer receptors and mRNA transcripts for granzymes and perforin. *Stress* 2005; **8**: 107-116 [PMID: 16019602 DOI: 10.1080/10253890500140972]

57 **Sacerdote P**, Manfredi B, Bianchi M, Panerai AE. Intermittent but not continuous inescapable footshock stress affects immune responses and immunocyte beta-endorphin concentrations in the rat. *Brain Behav Immun* 1994; **8**: 251-260 [PMID: 7865896 DOI: 10.1006/brbi.1994.1023]

58 **Shavit Y**, Martin FC, Yirmiya R, Ben-Eliyahu S, Terman GW, Weiner H, Gale RP, Liebeskind JC. Effects of a single administration of morphine or footshock stress on natural killer cell cytotoxicity. *Brain Behav Immun* 1987; **1**: 318-328 [PMID: 3453207]

59 **Bar-Yosef S**, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu S. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. *Anesthesiology* 2001; **94**: 1066-1073 [PMID: 11465599]

60 **Lewis JW**, Shavit Y, Terman GW, Nelson LR, Gale RP, Liebeskind JC. Apparent involvement of opioid peptides in stress-induced enhancement of tumor growth. *Peptides* 1983; **4**: 635-638 [PMID: 6686324]

61 **Sharify A**, Mahmoudi M, Izad MH, Hosseini MJ, Sharify M. Effect of acute pain on splenic NK cell activity, lymphocyte proliferation and cytokine production activities. *Immunopharmacol Immunotoxicol* 2007; **29**: 465-476 [PMID: 18075858 DOI: 10.1080/08923970701619877]

62 **Page GG**. Acute pain and immune impairment. *Pain Clin Updates* 2005; **13**: 1-4

63 **Snyder GL**, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. *Br J Anaesth* 2010; **105**: 106-115 [PMID: 20627881 DOI: 10.1093/bja/aeq164]

64 **Lundy J**, Lovett EJ, Hamilton S, Conran P. Halothane, surgery, immunosuppression and artificial pulmonary metastases. *Cancer* 1978; **41**: 827-830 [PMID: 638970]

65 **Shapiro J**, Jersky J, Katzav S, Feldman M, Segal S. Anesthetic drugs accelerate the progression of postoperative metastases of mouse tumors. *J Clin Invest* 1981; **68**: 678-685 [PMID: 7276167]

66 **Urner M**, Limbach LK, Herrmann IK, Müller-Edenborn B, Roth-Z'Graggen B, Schlicker A, Reyes L, Booy C, Hasler M, Stark WJ, Beck-Schimmer B. Fluorinated groups mediate the immunomodulatory effects of volatile anesthetics in acute cell injury. *Am J Respir Cell Mol Biol* 2011; **45**: 617-624 [PMID: 21239603 DOI: 10.1165/rcmb.2010-0451OC]

67 **Kurosawa S**, Kato M. Anesthetics, immune cells, and immune responses. *J Anesth* 2008; **22**: 263-277 [PMID: 18685933 DOI: 10.1007/s00540-008-0626-2]

68 **Saad MM**, Eom W, Hu G, Kim SJ, Crystal GJ. Persistency and pathway of isoflurane-induced inhibition of superoxide production by neutrophils. *Can J Anaesth* 2010; **57**: 50-57 [PMID: 19882198 DOI: 10.1007/s12630-009-9205-8]

69 **Biao Z**, Zhanggang X, Hao J, Changhong M, Jing C. The in vitro effect of desflurane preconditioning on endothelial adhesion molecules and mRNA expression. *Anesth Analg* 2005; **100**: 1007-1013 [PMID: 15781515 DOI: 10.1213/01.ANE.0000146432.39090.D4]

70 **Hu G**, Vinten-Johansen J, Salem MR, Zhao ZQ, Crystal GJ. Isoflurane inhibits neutrophil-endothelium interactions in the coronary circulation: lack of a role for adenosine triphosphate-sensitive potassium channels. *Anesth Analg* 2002; **94**: 849-56, table of contents [PMID: 11916783]

71 **Drenger B**, Gozal Y, Ginosar Y, Tochner Z, Chevion M. Halothane modifies oxygen free radical activity on the voltage-sensitive calcium channels in canine myocardial membranes. *Ann Card Anaesth* 1999; **2**: 16-21 [PMID: 17846486]

72 **Benzonana LL**, Perry NJ, Watts HR, Yang B, Perry IA, Coombes C, Takata M, Ma D. Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential via the hypoxia-inducible factor cellular signaling pathway in vitro. *Anesthesiology* 2013; **119**: 593-605 [PMID: 23774231 DOI: 10.1097/ALN.0b013e31829e47fd]

73 **Hyvärinen J**, Hassinen IE, Sormunen R, Mäki JM, Kivirikko KI, Koivunen P, Myllyharju J. Hearts of hypoxia-inducible factor prolyl 4-hydroxylase-2 hypomorphic mice show protection against acute ischemia-reperfusion injury. *J Biol Chem* 2010; **285**: 13646-13657 [PMID: 20185832 DOI: 10.1074/jbc.M109.084855]

74 **Bautista L**, Castro MJ, López-Barneo J, Castellano A. Hypoxia inducible factor-2alpha stabilization and maxi-K+ channel beta1-subunit gene repression by hypoxia in cardiac myocytes: role in preconditioning. *Circ Res* 2009; **104**: 1364-1372 [PMID: 19461047 DOI: 10.1161/CIRCRESAHA.108.190645]

75 **Prabhakar NR**, Semenza GL. Adaptive and maladaptive cardiorespiratory responses to continuous and intermittent hypoxia mediated by hypoxia-inducible factors 1 and 2. *Physiol Rev* 2012; **92**: 967-1003 [PMID: 22811423 DOI: 10.1152/physrev.00030.2011]

76 **Ma D**, Lim T, Xu J, Tang H, Wan Y, Zhao H, Hossain M, Maxwell PH, Maze M. Xenon preconditioning protects against renal ischemic-reperfusion injury via HIF-1alpha activation. *J Am Soc Nephrol* 2009; **20**: 713-720 [PMID: 19144758 DOI: 10.1681/ASN.2008070712]

77 **Zitta K**, Meybohm P, Bein B, Ohnesorge H, Steinfath M, Scholz J, Albrecht M. Cytoprotective effects of the volatile anesthetic sevoflurane are highly dependent on timing and duration of sevoflurane conditioning: findings from a human, in-vitro hypoxia model. *Eur J Pharmacol* 2010; **645**: 39-46 [PMID: 20655305 DOI: 10.1016/j.ejphar.2010.07.017]

78 **Lang XE**, Wang X, Jin JH. Mechanisms of cardioprotection by isoflurane against I/R injury. *Front Biosci* (Landmark Ed) 2013; **18**: 387-393 [PMID: 23276931]

79 **Zhang L**, Huang H, Cheng J, Liu J, Zhao H, Vizcaychipi MP, Ma D. Pre-treatment with isoflurane ameliorates renal ischemic-reperfusion injury in mice. *Life Sci* 2011; **88**: 1102-1107 [PMID: 21565202 DOI: 10.1016/j.lfs.2011.04.004]

80 **Müller-Edenborn B**, Roth-Z'graggen B, Bartnicka K, Borgeat A, Hoos A, Borsig L, Beck-Schimmer B. Volatile anesthetics reduce invasion of colorectal cancer cells through down-regulation of matrix metalloproteinase-9. *Anesthesiology* 2012; **117**: 293-301 [PMID: 22739763 DOI: 10.1097/ALN.0b013e3182605df1]

81 **Yuki K**, Astrof NS, Bracken C, Soriano SG, Shimaoka M. Sevoflurane binds and allosterically blocks integrin lymphocyte function-associated antigen-1. *Anesthesiology* 2010; **113**: 600-609 [PMID: 20693879 DOI: 10.1097/ALN.0b013e3181e89a77]

82 **Yuki K**, Astrof NS, Bracken C, Yoo R, Silkworth W, Soriano SG, Shimaoka M. The volatile anesthetic isoflurane perturbs conformational activation of integrin LFA-1 by binding to the allosteric regulatory cavity. *FASEB J* 2008; **22**: 4109-4116 [PMID: 18708587 DOI: 10.1096/fj.08-113324]

83 **Loop T**, Dovi-Akue D, Frick M, Roesslein M, Egger L, Humar M, Hoetzel A, Schmidt R, Borner C, Pahl HL, Geiger KK, Pannen BH. Volatile anesthetics induce caspase-dependent, mitochondria-mediated apoptosis in human T lymphocytes in vitro. *Anesthesiology* 2005; **102**: 1147-1157 [PMID: 15915027]

84 **Rem J**, Brandt MR, Kehlet H. Prevention of postoperative lymphopenia and granulocytosis by epidural analgesia. *Lancet* 1980; **1**: 283-284 [PMID: 6101739]

85 **Vallejo R**, Hord ED, Barna SA, Santiago-Palma J, Ahmed S. Perioperative immunosuppression in cancer patients. *J Environ Pathol Toxicol Oncol* 2003; **22**: 139-146 [PMID: 14533877]

86 **Woods GM**, Griffiths DM. Reversible inhibition of natural killer cell activity by volatile anaesthetic agents in vitro. *Br J Anaesth* 1986; **58**: 535-539 [PMID: 3457589]

87 **Markovic SN**, Knight PR, Murasko DM. Inhibition of interferon stimulation of natural killer cell activity in mice anesthetized with halothane or isoflurane. *Anesthesiology* 1993; **78**: 700-706 [PMID: 8466070]

88 **Tønnesen E**, Brinkløv MM, Christensen NJ, Olesen AS, Madsen T. Natural killer cell activity and lymphocyte function during and after coronary artery bypass grafting in relation to the endocrine stress response. *Anesthesiology* 1987; **67**: 526-533 [PMID: 3499099]

89 **Markovic SN**, Murasko DM. Anesthesia inhibits interferon-induced natural killer cell cytotoxicity via induction of CD8+ suppressor cells. *Cell Immunol* 1993; **151**: 474-480 [PMID: 8402951 DOI: 10.1006/cimm.1993.1256]

90 **Braz MG**, Mazoti MÁ, Giacobino J, Braz LG, Golim Mde A, Ferrasi AC, de Carvalho LR, Braz JR, Salvadori DM. Genotoxicity, cytotoxicity and gene expression in patients undergoing elective surgery under isoflurane anaesthesia. *Mutagenesis* 2011; **26**: 415-420 [PMID: 21257718 DOI: 10.1093/mutage/geq109]

91 **Musak L**, Smerhovsky Z, Halasova E, Osina O, Letkova L, Vodickova L, Polakova V, Buchancova J, Hemminki K, Vodicka P. Chromosomal damage among medical staff occupationally exposed to volatile anesthetics, antineoplastic drugs, and formaldehyde. *Scand J Work Environ Health* 2013; **39**: 618-630 [PMID: 23525098 DOI: 10.5271/sjweh.3358]

92 **Heine J**, Leuwer M, Scheinichen D, Arseniev L, Jaeger K, Piepenbrock S. Flow cytometry evaluation of the in vitro influence of four i.v. anaesthetics on respiratory burst of neutrophils. *Br J Anaesth* 1996; **77**: 387-392 [PMID: 8949817]

93 **Melamed R**, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. *Anesth Analg* 2003; **97**: 1331-1339 [PMID: 14570648]

94 **Salo M**, Pirttikangas CO, Pulkki K. Effects of propofol emulsion and thiopentone on T helper cell type-1/type-2 balance in vitro. *Anaesthesia* 1997; **52**: 341-344 [PMID: 9135186]

95 **Chen RM**, Wu CH, Chang HC, Wu GJ, Lin YL, Sheu JR, Chen TL. Propofol suppresses macrophage functions and modulates mitochondrial membrane potential and cellular adenosine triphosphate synthesis. *Anesthesiology* 2003; **98**: 1178-1185 [PMID: 12717140]

96 **Heller A**, Heller S, Blecken S, Urbaschek R, Koch T. Effects of intravenous anesthetics on bacterial elimination in human blood in vitro. *Acta Anaesthesiol Scand* 1998; **42**: 518-526 [PMID: 9605366]

97 **Wu GJ**, Tai YT, Chen TL, Lin LL, Ueng YF, Chen RM. Propofol specifically inhibits mitochondrial membrane potential but not complex I NADH dehydrogenase activity, thus reducing cellular ATP biosynthesis and migration of macrophages. *Ann N Y Acad Sci* 2005; **1042**: 168-176 [PMID: 15965060 DOI: 10.1196/annals.1338.019]

98 **Hardwick M**, Fertikh D, Culty M, Li H, Vidic B, Papadopoulos V. Peripheral-type benzodiazepine receptor (PBR) in human breast cancer: correlation of breast cancer cell aggressive phenotype with PBR expression, nuclear localization, and PBR-mediated cell proliferation and nuclear transport of cholesterol. *Cancer Res* 1999; **59**: 831-842 [PMID: 10029072]

99 **Garib V**, Niggemann B, Zänker KS, Brandt L, Kubens BS. Influence of non-volatile anesthetics on the migration behavior of the human breast cancer cell line MDA-MB-468. *Acta Anaesthesiol Scand* 2002; **46**: 836-844 [PMID: 12139540]

100 **Katzav S**, Shapiro J, Segal S, Feldman M. General anesthesia during excision of a mouse tumor accelerates postsurgical growth of metastases by suppression of natural killer cell activity. *Isr J Med Sci* 1986; **22**: 339-345 [PMID: 3744781]

101 **Bentley MW**, Stas JM, Johnson JM, Viet BC, Garrett N. Effects of preincisional ketamine treatment on natural killer cell activity and postoperative pain management after oral maxillofacial surgery. *AANA J* 2005; **73**: 427-436 [PMID: 16355944]

102 **Singleton PA**, Moreno-Vinasco L, Sammani S, Wanderling SL, Moss J, Garcia JG. Attenuation of vascular permeability by methylnaltrexone: role of mOP-R and S1P3 transactivation. *Am J Respir Cell Mol Biol* 2007; **37**: 222-231 [PMID: 17395891 DOI: 10.1165/rcmb.2006-0327OC]

103 **Singleton PA**, Moss J. Effect of perioperative opioids on cancer recurrence: a hypothesis. *Future Oncol* 2010; **6**: 1237-1242 [PMID: 20799870 DOI: 10.2217/fon.10.99]

104 **Carr DJ**, Rogers TJ, Weber RJ. The relevance of opioids and opioid receptors on immunocompetence and immune homeostasis. *Proc Soc Exp Biol Med* 1996; **213**: 248-257 [PMID: 8985308]

105 **Flores LR**, Dretchen KL, Bayer BM. Potential role of the autonomic nervous system in the immunosuppressive effects of acute morphine administration. *Eur J Pharmacol* 1996; **318**: 437-446 [PMID: 9016936]

106 **Freier DO**, Fuchs BA. A mechanism of action for morphine-induced immunosuppression: corticosterone mediates morphine-induced suppression of natural killer cell activity. *J Pharmacol Exp Ther* 1994; **270**: 1127-1133 [PMID: 7932161]

107 **Bryant HU**, Bernton EW, Kenner JR, Holaday JW. Role of adrenal cortical activation in the immunosuppressive effects of chronic morphine treatment. *Endocrinology* 1991; **128**: 3253-3258 [PMID: 2036988]

108 **Mellon RD**, Bayer BM. Evidence for central opioid receptors in the immunomodulatory effects of morphine: review of potential mechanism(s) of action. *J Neuroimmunol* 1998; **83**: 19-28 [PMID: 9610669]

109 **Shavit Y**, Ben-Eliyahu S, Zeidel A, Beilin B. Effects of fentanyl on natural killer cell activity and on resistance to tumor metastasis in rats. Dose and timing study. *Neuroimmunomodulation* 2004; **11**: 255-260 [PMID: 15249732 DOI: 10.1159/000078444]

110 **Li W**, Tang HZ, Jiang YB, Xu MX. [Influence of different doses of fentanyl on T-lymphocyte subpopulations and natural killer cells of patients with esophageal tumor during preoperation and postoperation]. *Aizheng* 2003; **22**: 634-636 [PMID: 12948416]

111 **Jaeger K**, Scheinichen D, Heine J, André M, Bund M, Piepenbrock S, Leuwer M. Remifentanil, fentanyl, and alfentanil have no influence on the respiratory burst of human neutrophils in vitro. *Acta Anaesthesiol Scand* 1998; **42**: 1110-1113

[PMID: 9809098]
112 **Gaspani L**, Bianchi M, Limiroli E, Panerai AE, Sacerdote P. The analgesic drug tramadol prevents the effect of surgery on natural killer cell activity and metastatic colonization in rats. *J Neuroimmunol* 2002; **129**: 18-24 [PMID: 12161016]
113 **Liu YM**, Zhu SM, Wang KR, Feng ZY, Chen QL. Effect of tramadol on immune responses and nociceptive thresholds in a rat model of incisional pain. *Zhejiang Daxue Kexue Zazhi B* 2008; **9**: 895-902 [PMID: 18988309 DOI: 10.1631/jzus.B0820039]
114 **Sacerdote P**, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, Ammatuna M, Panerai AE. The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesth Analg* 2000; **90**: 1411-1414 [PMID: 10825330]
115 **McLaughlin PJ**, Zagon IS. The opioid growth factor-opioid growth factor receptor axis: homeostatic regulator of cell proliferation and its implications for health and disease. *Biochem Pharmacol* 2012; **84**: 746-755 [PMID: 22687282 DOI: 10.1016/j.bcp.2012.05.018]
116 **Spirkoski J**, Melo FR, Grujic M, Calounova G, Lundequist A, Wernersson S, Pejler G. Mast cell apoptosis induced by siramesine, a sigma-2 receptor agonist. *Biochem Pharmacol* 2012; **84**: 1671-1680 [PMID: 23058984 DOI: 10.1016/j.bcp.2012.09.028]
117 **Stefano GB**, Kream RM, Mantione KJ, Sheehan M, Cadet P, Zhu W, Bilfinger TV, Esch T. Endogenous morphine/nitric oxide-coupled regulation of cellular physiology and gene expression: implications for cancer biology. *Semin Cancer Biol* 2008; **18**: 199-210 [PMID: 18203618 DOI: 10.1016/j.semcancer.2007.12.003]
118 **Cadet P**, Rasmussen M, Zhu W, Tonnesen E, Mantione KJ, Stefano GB. Endogenous morphinergic signaling and tumor growth. *Front Biosci* 2004; **9**: 3176-3186 [PMID: 15353348]
119 **Tegeder I**, Grösch S, Schmidtko A, Häussler A, Schmidt H, Niederberger E, Scholich K, Geisslinger G. G protein-independent G1 cell cycle block and apoptosis with morphine in adenocarcinoma cells: involvement of p53 phosphorylation. *Cancer Res* 2003; **63**: 1846-1852 [PMID: 12702572]
120 **Tsujikawa H**, Shoda T, Mizota T, Fukuda K. Morphine induces DNA damage and P53 activation in CD3+ T cells. *Biochim Biophys Acta* 2009; **1790**: 793-799 [PMID: 19397953 DOI: 10.1016/j.bbagen.2009.04.011]
121 **Yin D**, Woodruff M, Zhang Y, Whaley S, Miao J, Ferslew K, Zhao J, Stuart C. Morphine promotes Jurkat cell apoptosis through pro-apoptotic FADD/P53 and anti-apoptotic PI3K/Akt/NF-kappaB pathways. *J Neuroimmunol* 2006; **174**: 101-107 [PMID: 16529824 DOI: 10.1016/j.jneuroim.2006.02.001]
122 **Qin Y**, Chen J, Li L, Liao CJ, Liang YB, Guan EJ, Xie YB. Exogenous morphine inhibits human gastric cancer MGC-803 cell growth by cell cycle arrest and apoptosis induction. *Asian Pac J Cancer Prev* 2012; **13**: 1377-1382 [PMID: 22799335]
123 **Gach K**, Wyrębska A, Fichna J, Janecka A. The role of morphine in regulation of cancer cell growth. *Naunyn Schmiedebergs Arch Pharmacol* 2011; **384**: 221-230 [PMID: 21800094 DOI: 10.1007/s00210-011-0672-4]
124 **Chen YL**, Law PY, Loh HH. The other side of the opioid story: modulation of cell growth and survival signaling. *Curr Med Chem* 2008; **15**: 772-778 [PMID: 18393846]
125 **Yeager MP**, Colacchio TA. Effect of morphine on growth of metastatic colon cancer in vivo. *Arch Surg* 1991; **126**: 454-456 [PMID: 2009060]
126 **Page GG**, Ben-Eliyahu S, Yirmiya R, Liebeskind JC. Morphine attenuates surgery-induced enhancement of metastatic colonization in rats. *Pain* 1993; **54**: 21-28 [PMID: 8378099]
127 **Page GG**, Ben-Eliyahu S, Liebeskind JC. The role of LGL/NK cells in surgery-induced promotion of metastasis and its attenuation by morphine. *Brain Behav Immun* 1994; **8**: 241-250 [PMID: 7865895]
128 **Tarhini AA**, Cherian J, Moschos SJ, Tawbi HA, Shuai Y, Gooding WE, Sander C, Kirkwood JM. Safety and efficacy of combination immunotherapy with interferon alfa-2b and tremelimumab in patients with stage IV melanoma. *J Clin Oncol* 2012; **30**: 322-328 [PMID: 22184371 DOI: 10.1200/JCO.2011.37.5394]
129 **Van Gool AR**, Van Ojik HH, Kruit WH, Mulder PG, Fekkes D, Bannink M, Scharpé S, Stoter G, Eggermont AM, Maes M, Verkerk R. Serum activity of prolyl endopeptidase, but not of dipeptidyl peptidase IV, is decreased by immunotherapy with IFN-alpha in high-risk melanoma patients. *J Interferon Cytokine Res* 2004; **24**: 411-415 [PMID: 15296652 DOI: 10.1089/1079990041535629]
130 **Van Gool AR**, Verkerk R, Fekkes D, Sleijfer S, Bannink M, Kruit WH, van der Holt B, Scharpé S, Eggermont AM, Stoter G, Hengeveld MW. Plasma activity of prolyl endopeptidase in relation to psychopathology during immunotherapy with IFN-alpha in patients with renal cell carcinoma. *J Interferon Cytokine Res* 2008; **28**: 283-286 [PMID: 18547158 DOI: 10.1089/jir.2007.0058]
131 **Hollmann MW**, Gross A, Jelacin N, Durieux ME. Local anesthetic effects on priming and activation of human neutrophils. *Anesthesiology* 2001; **95**: 113-122 [PMID: 11465548]
132 **Johnson SM**, Saint John BE, Dine AP. Local anesthetics as antimicrobial agents: a review. *Surg Infect* (Larchmt) 2008; **9**: 205-213 [PMID: 18426354 DOI: 10.1089/sur.2007.036]
133 **Di Padova M**, Barbieri R, Fanciulli M, Arcuri E, Floridi A. Effect of local anesthetic ropivacaine on the energy metabolism of Ehrlich ascites tumor cells. *Oncol Res* 1998; **10**: 491-498 [PMID: 10338152]
134 **Mammoto T**, Higashiyama S, Mukai M, Mammoto A, Ayaki M, Mashimo T, Hayashi Y, Kishi Y, Nakamura H, Akedo H. Infiltration anesthetic lidocaine inhibits cancer cell invasion by modulating ectodomain shedding of heparin-binding epidermal growth factor-like growth factor (HB-EGF). *J Cell Physiol* 2002; **192**: 351-358 [PMID: 12124780 DOI: 10.1002/jcp.10145]
135 **Villar-Garea A**, Fraga MF, Espada J, Esteller M. Procaine is a DNA-demethylating agent with growth-inhibitory effects in human cancer cells. *Cancer Res* 2003; **63**: 4984-4989 [PMID: 12941824]
136 **Piegeler T**, Votta-Velis EG, Liu G, Place AT, Schwartz DE, Beck-Schimmer B, Minshall RD, Borgeat A. Antimetastatic potential of amide-linked local anesthetics: inhibition of lung adenocarcinoma cell migration and inflammatory Src signaling independent of sodium channel blockade. *Anesthesiology* 2012; **117**: 548-559 [PMID: 22846676 DOI: 10.1097/ALN.0b013e3182661977]
137 **Pastrone I**, Viale M, Cafaggi S, Mariggiò MA, Parodi A, Esposito M. Effect of the cisplatin-procaine complex DPR in combination with several anticancer agents on murine P388 leukemic cells in vitro and in vivo. *Invest New Drugs* 1998; **16**: 297-302 [PMID: 10426661]
138 **Viale M**, Pastrone I, Pellecchia C, Vannozzi MO, Cafaggi S, Esposito M. Combination of cisplatin-procaine complex DPR with anticancer drugs increases cytotoxicity against ovarian cancer cell lines. *Anticancer Drugs* 1998; **9**: 457-463 [PMID: 9660544]
139 **Fleshner M**, Bellgrau D, Watkins LR, Laudenslager ML, Maier SF. Stress-induced reduction in the rat mixed lymphocyte reaction is due to macrophages and not to changes in T cell phenotypes. *J Neuroimmunol* 1995; **56**: 45-52 [PMID: 7822481]
140 **Laudenslager ML**, Fleshner M, Hofstadter P, Held PE, Simons L, Maier SF. Suppression of specific antibody production by inescapable shock: stability under varying conditions. *Brain Behav Immun* 1988; **2**: 92-101 [PMID: 3148338]
141 **Page GG**, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. *Pain* 2001; **90**: 191-199 [PMID: 11166986]
142 **Wada H**, Seki S, Takahashi T, Kawarabayashi N, Higuchi H, Habu Y, Sugahara S, Kazama T. Combined spinal and general anesthesia attenuates liver metastasis by preserving

TH1/TH2 cytokine balance. *Anesthesiology* 2007; **106**: 499-506 [PMID: 17325508]
143 **Deegan CA**, Murray D, Doran P, Ecimovic P, Moriarty DC, Buggy DJ. Effect of anaesthetic technique on oestrogen receptor-negative breast cancer cell function in vitro. *Br J Anaesth* 2009; **103**: 685-690 [PMID: 19776028 DOI: 10.1093/bja/aep261]
144 **Exadaktylos AK**, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 2006; **105**: 660-664 [PMID: 17006061]
145 **Ochroch EA**, Fleisher LA. Retrospective analysis: looking backward to point the way forward. *Anesthesiology* 2006; **105**: 643-644 [PMID: 17006057]
146 **Haller G**, Myles PS. Regional block and cancer recurrence: too early to tell. *Anesthesiology* 2007; **107**: 354; author reply 354-355 [PMID: 17667583 DOI: 10.1097/01.anes.0000271919.18782.f4]
147 **Biki B**, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology* 2008; **109**: 180-187 [PMID: 18648226 DOI: 10.1097/ALN.0b013e31817f5b73]
148 **Daley MD**, Norman PH. Retrospective but not rigorous. *Anesthesiology* 2009; **111**: 203; author reply 203-204 [PMID: 19546695 DOI: 10.1097/ALN.0b013e3181a85e66]
149 **Le Cras AE**, Galley HF, Webster NR. Spinal but not general anesthesia increases the ratio of T helper 1 to T helper 2 cell subsets in patients undergoing transurethral resection of the prostate. *Anesth Analg* 1998; **87**: 1421-1425 [PMID: 9842841]
150 **Wuethrich PY**, Thalmann GN, Studer UE, Burkhard FC. Epidural analgesia during open radical prostatectomy does not improve long-term cancer-related outcome: a retrospective study in patients with advanced prostate cancer. *PLoS One* 2013; **8**: e72873 [PMID: 23977366 DOI: 10.1371/journal.pone.0072873]
151 **Retsky M**, Rogers R, Demicheli R, Hrushesky WJ, Gukas I, Vaidya JS, Baum M, Forget P, Dekock M, Pachmann K. NSAID analgesic ketorolac used perioperatively may suppress early breast cancer relapse: particular relevance to triple negative subgroup. *Breast Cancer Res Treat* 2012; **134**: 881-888 [PMID: 22622810 DOI: 10.1007/s10549-012-2094-5]
152 **Tsui BC**, Rashiq S, Schopflocher D, Murtha A, Broemling S, Pillay J, Finucane BT. Epidural anesthesia and cancer recurrence rates after radical prostatectomy. *Can J Anaesth* 2010; **57**: 107-112 [PMID: 19911247 DOI: 10.1007/s12630-009-9214-7]
153 **Sessler DI**. Regional anesthesia and prostate cancer recurrence. *Can J Anaesth* 2010; **57**: 99-102 [PMID: 20041356 DOI: 10.1007/s12630-009-9222-7]
154 **Cummings KC**, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. *Anesthesiology* 2012; **116**: 797-806 [PMID: 22273991 DOI: 10.1097/ALN.0b013e31824674f6]
155 **Gupta A**, Björnsson A, Fredriksson M, Hallböök O, Eintrei C. Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in central Sweden. *Br J Anaesth* 2011; **107**: 164-170 [PMID: 21586443 DOI: 10.1093/bja/aer100]
156 **Christopherson R**, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. *Anesth Analg* 2008; **107**: 325-332 [PMID: 18635504 DOI: 10.1213/ane.0b013e3181770f55]
157 **Gottschalk A**, Ford JG, Regelin CC, You J, Mascha EJ, Sessler DI, Durieux ME, Nemergut EC. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. *Anesthesiology* 2010; **113**: 27-34 [PMID: 20508494 DOI: 10.1097/ALN.0b013e3181de6d0d]
158 **Forget P**, Leonard D, Kartheuser A, De Kock M. Endpoint selection and unreported analgesic use may render oncologic studies inconclusive. *Anesthesiology* 2011; **114**: 717; author reply 718 [PMID: 21343728 DOI: 10.1097/ALN.0b013e3182084b18]
159 **Merquiol F**, Montelimard AS, Nourissat A, Molliex S, Zufferey PJ. Cervical epidural anesthesia is associated with increased cancer-free survival in laryngeal and hypopharyngeal cancer surgery: a retrospective propensity-matched analysis. *Reg Anesth Pain Med* 2013; **38**: 398-402 [PMID: 23881179 DOI: 10.1097/AAP.0b013e31829cc3fb]
160 **Schlagenhauff B**, Ellwanger U, Breuninger H, Stroebel W, Rassner G, Garbe C. Prognostic impact of the type of anaesthesia used during the excision of primary cutaneous melanoma. *Melanoma Res* 2000; **10**: 165-169 [PMID: 10803717]
161 **Lacassie HJ**, Cartagena J, Brañes J, Assel M, Echevarría GC. The relationship between neuraxial anesthesia and advanced ovarian cancer-related outcomes in the Chilean population. *Anesth Analg* 2013; **117**: 653-660 [PMID: 23868889 DOI: 10.1213/ANE.0b013e3182a07046]
162 **Binczak M**, Tournay E, Billard V, Rey A, Jayr C. Major abdominal surgery for cancer: does epidural analgesia have a long-term effect on recurrence-free and overall survival? *Ann Fr Anesth Reanim* 2013; **32**: e81-e88 [PMID: 23618609 DOI: 10.1016/j.annfar.2013.02.027]
163 **Chen WK**, Miao CH. The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. *PLoS One* 2013; **8**: e56540 [PMID: 23437162 DOI: 10.1371/journal.pone.0056540]
164 **Oppfeldt A**, Carlsson P. The Effect of Paravertebral Block During Surgery on the Recurrence of Breast Cancer. Abstract A4253. American Society of Anesthesiologists. San Francisco, CA, 2013. Available from: URL: http://www.asaabstracts.com
165 **Weber RS**, Jabbour N, Martin RC. Anemia and transfusions in patients undergoing surgery for cancer. *Ann Surg Oncol* 2008; **15**: 34-45 [PMID: 17943390 DOI: 10.1245/s10434-007-9502-9]
166 **Blajchman MA**. Transfusion-associated immunomodulation and universal white cell reduction: are we putting the cart before the horse? *Transfusion* 1999; **39**: 665-670 [PMID: 10413271]
167 **Kaplan J**, Sarnaik S, Gitlin J, Lusher J. Diminished helper/suppressor lymphocyte ratios and natural killer activity in recipients of repeated blood transfusions. *Blood* 1984; **64**: 308-310 [PMID: 6234037]
168 **Brunson ME**, Alexander JW. Mechanisms of transfusion-induced immunosuppression. *Transfusion* 1990; **30**: 651-658 [PMID: 2205953]
169 **Blajchman MA**, Bardossy L, Carmen R, Sastry A, Singal DP. Allogeneic blood transfusion-induced enhancement of tumor growth: two animal models showing amelioration by leukodepletion and passive transfer using spleen cells. *Blood* 1993; **81**: 1880-1882 [PMID: 8461473]
170 **Ydy LR**, Slhessarenko N, de Aguilar-Nascimento JE. Effect of perioperative allogeneic red blood cell transfusion on the immune-inflammatory response after colorectal cancer resection. *World J Surg* 2007; **31**: 2044-2051 [PMID: 17671807 DOI: 10.1007/s00268-007-9159-3]
171 **Chen G**, Zhang FJ, Gong M, Yan M. Effect of perioperative autologous versus allogeneic blood transfusion on the immune system in gastric cancer patients. *J Zhejiang Univ Sci B* 2007; **8**: 560-565 [PMID: 17657857 DOI: 10.1631/jzus.2007.B0560]
172 **Vamvakas EC**, Carven JH. Allogeneic blood transfusion, hospital charges, and length of hospitalization: a study of 487 consecutive patients undergoing colorectal cancer resection. *Arch Pathol Lab Med* 1998; **122**: 145-151 [PMID: 9499357]
173 **Ling FC**, Hoelscher AH, Vallböhmer D, Schmidt D, Picker S, Gathof BS, Bollschweiler E, Schneider PM. Leukocyte depletion in allogeneic blood transfusion does not change the negative influence on survival following transthoracic resection for esophageal cancer. *J Gastrointest Surg* 2009; **13**:

581-586 [PMID: 19152023 DOI: 10.1007/s11605-008-0787-1]
174 **Busch OR**, Hop WC, Hoynck van Papendrecht MA, Marquet RL, Jeekel J. Blood transfusions and prognosis in colorectal cancer. *N Engl J Med* 1993; **328**: 1372-1376 [PMID: 8292113 DOI: 10.1056/NEJM199305133281902]
175 **Heiss MM**, Mempel W, Delanoff C, Jauch KW, Gabka C, Mempel M, Dieterich HJ, Eissner HJ, Schildberg FW. Blood transfusion-modulated tumor recurrence: first results of a randomized study of autologous versus allogeneic blood transfusion in colorectal cancer surgery. *J Clin Oncol* 1994; **12**: 1859-1867 [PMID: 8083709]
176 **Houbiers JG**, Brand A, van de Watering LM, Hermans J, Verwey PJ, Bijnen AB, Pahlplatz P, Eeftinck Schattenkerk M, Wobbes T, de Vries JE. Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. *Lancet* 1994; **344**: 573-578 [PMID: 7914960]
177 **Beilin B**, Martin FC, Shavit Y, Gale RP, Liebeskind JC. Suppression of natural killer cell activity by high-dose narcotic anesthesia in rats. *Brain Behav Immun* 1989; **3**: 129-137 [PMID: 2477090]
178 **Colacchio TA**, Yeager MP, Hildebrandt LW. Perioperative immunomodulation in cancer surgery. *Am J Surg* 1994; **167**: 174-179 [PMID: 8311130]
179 **Ben-Eliyahu S**. The price of anticancer intervention. Does surgery promote metastasis? *Lancet Oncol* 2002; **3**: 578-579 [PMID: 12233735]
180 **Grytli HH**, Fagerland MW, Fosså SD, Taskén KA, Håheim LL. Use of β-blockers is associated with prostate cancer-specific survival in prostate cancer patients on androgen deprivation therapy. *Prostate* 2013; **73**: 250-260 [PMID: 22821802 DOI: 10.1002/pros.22564]
181 **Wang HM**, Liao ZX, Komaki R, Welsh JW, O'Reilly MS, Chang JY, Zhuang Y, Levy LB, Lu C, Gomez DR. Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy. *Ann Oncol* 2013; **24**: 1312-1319 [PMID: 23300016 DOI: 10.1093/annonc/mds616]
182 **Barron TI**, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: a population- based study. *J Clin Oncol* 2011; **29**: 2635-2644 [PMID: 21632503 DOI: 10.1200/JCO.2010.33.5422]
183 **Melhem-Bertrandt A**, Chavez-Macgregor M, Lei X, Brown EN, Lee RT, Meric-Bernstam F, Sood AK, Conzen SD, Hortobagyi GN, Gonzalez-Angulo AM. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. *J Clin Oncol* 2011; **29**: 2645-2652 [PMID: 21632501 DOI: 10.1200/JCO.2010.33.4441]
184 **Ben-Eliyahu S**, Shakhar G, Rosenne E, Levinson Y, Beilin B. Hypothermia in barbiturate-anesthetized rats suppresses natural killer cell activity and compromises resistance to tumor metastasis: a role for adrenergic mechanisms. *Anesthesiology* 1999; **91**: 732-740 [PMID: 10485785]
185 **Beilin B**, Shavit Y, Razumovsky J, Wolloch Y, Zeidel A, Bessler H. Effects of mild perioperative hypothermia on cellular immune responses. *Anesthesiology* 1998; **89**: 1133-1140 [PMID: 9822001]
186 **Stefanski V**, Ben-Eliyahu S. Social confrontation and tumor metastasis in rats: defeat and beta-adrenergic mechanisms. *Physiol Behav* 1996; **60**: 277-282 [PMID: 8804676]

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