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Anesthetic Considerations for Management of Cancer Patients to Decrease Cancer Recurrence

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Abstract

Alongside the known direct, short-term effects of anesthesia in general, there is emerging evidence of an immunomodulatory effect with specific anesthetics that may decrease patient's defences against malignant neoplastic growths. This effect is especially important in the setting of surgical management of neoplasms, which is often the best option for long-term survival in patients with solid neoplasm. Many studies have speculated on the best anesthetic technique to reduce the neoplasm recurrence and promote patient survival, however, we often neglect the sympathetic stress response to neoplasia and how anesthetics modulate this effect. In this review, we study the evidence as it pertains to anesthetic techniques and pain control, particularly general vs. regional anesthesia, and opioid analgesia. At this time there is not enough evidence to support that regional anesthesia has a more favorable outcome than general anesthesia, or that opioids should not be used in neoplasm-related pain management because of their potential pro-metastatic properties secondary to opioid-induced immunosuppression. Instead, the debate over anesthetic use should be centered on adequate pain control since overwhelming evidence have shown that pain-related stress reaction mediated via β-adrenergic activation, promotes neoplastic propagation and metastasis, hence decreasing survival rates.

Introduction

The use of anesthetics is commonplace in the perioperative setting for sedation, amnesia, analgesia, and immobilization. Alongside the known direct effects of anesthesia in general, there is emerging evidence of an immunomodulatory effect with specific anesthetics that may decrease host defenses against neoplastic growth. Analyzing the effect of the anesthesia on tumor growth, its propensity to metastasize, and its recurrence is an interesting idea that brings about new implications to a seemingly straight forward, routine anesthesia delivery. However, to study this potential long-term effect of anesthesia is complicated and difficult in methodology. Cancer recurrence is multifactorial, and the incidence of recurrence can vary substantially based upon the type of cancer, stage and grade at diagnosis, biologic characteristics of the tumor, initial treatment modalities, and host immune function. The ability of the immune system to restrict, and possible to eradicate neoplastic growth is especially significant in the setting of surgical management, which is often the best option for long-term survival in patients with solid tumors. Surgical resection, however, can inherently promote cancer metastasis or recurrence by the inadvertent release of tumor cells and humoral factors into the circulation and the normal surgical stress response may lead to metabolic and neuroendocrine changes that further inhibit host defenses against the implantation of circulating tumor cells [1,2]. Preservation of host immune function in the perioperative and intraoperative setting can lead to better patient outcomes and the minimization of risks, analogous to pre-operative optimization of any surgical patient. However, modulation of immune function has been shown to be influenced by anesthetic technique. This was demonstrated in *in vivo* and *in vitro*, in both manual models and with

the utilization of the human species but the vast majority of the studies focused on modulation of the short-term immunological responses by anesthetic techniques or compounds. However, it is unclear how these results translate into long-term outcome. The study of patient outcomes with different anesthetic techniques can be challenging, yet it may be essential to cause a change of practice in the surgical management of oncology patients. Here, we review most recent studies and attempt to chart a potential way in which anesthesia can modulate immune response in the long-term time frame via modulation of the sympathetic system. First, we will examine the effects of regional versus general anesthesia on the growth and recurrence of neoplasms.

The Effect of General Anesthesia on Cancer Recurrence

Wigmore et al. published a study in 2015 comparing mortality rates over 3 years after elective surgery in a comprehensive cancer center. In a retrospective analysis, they compared mortality after cancer surgery in more than 7,000 patients given volatile general anesthesia (INHA) or total intravenous anesthesia (TIVA) [3]. Patients in the TIVA group received sedation with propofol and remifentanil, while patients in the volatile anesthetic group received either sevoflurane or isoflurane, along with an adjunct opioid at the anesthesiologist's discretion. Variables included patient's age at the time of procedure, severity of malignancy, tumor site and group, intraoperative transfusion of blood products, severity of surgery, sex, height and weight, and the use of epidural analgesia, as these are all potentially confounding. The study by Wigmore et al. cannot estimate the effect of opioids since most the enrolled individuals received opioids. Such an effect would be difficult to estimate since medical provider had freedom to use to use different opioids in one arm versus remifentanil in another arm of the study. Perhaps the most significant limitation of the study is the uneven distribution of patients with more favorable prognosis and lack of the

tumor staging data. The patients who were expected to have better prognosis, such as breast cancer patients, had a lower proportion in the inhaled volatile anesthetic group [3].

Interestingly, results showed that the mortality was approximately 50% greater with volatile than with IV anesthesia, with an adjusted hazard ratio of 1.46 (1.29 to 1.66), no matter their ASA score, surgical severity, or whether the patient had metastasis at the time of the procedure [3]. The study, as with many studies of this nature, showed an association but not causation between the type of anesthetic delivered and survival rates. There is a need for further large and prospective studies to investigate this association, as well as the expansion of laboratory and animal studies to explore the possible biological mechanism. This study in particular, suggests the differential effect of volatile anesthetics versus TIVA on tumor progression, and potential implications of their effect on the immune system in the perioperative period [3].

Inherited limitations of the study by Wigmore et al. are difficult to overcome in a rigorous fashion. However, his observations are well aligned with studies from more than four decades ago, when the association between volatile anesthetics and neoplasm progression was first observed. Lundy et al. proposed that the combination of halothane, surgery and immunosuppression increased pulmonary metastases in mice inoculated with tumor cells [4]. Shapiro et al. found that lung tumor progression was accelerated in mouse models when exposed to halothane and nitrous oxide [5]. There are no human studies on the isolated effect of volatile anesthetics on tumor spread and metastasis. Nevertheless, since inhaled anesthetics have direct and indirect effects on different aspects of the immune response, it is reasonable to assert that they are important actors in postoperative immunosuppression and residual malignant cell migration and invasion.

Interestingly, recent evidence shows oxidative DNA damage induced by isoflurane in elective surgery suggesting that inhalation anesthesia could potentially trigger tumor growth. Coincidently, Musak et al. showed that healthcare personnel exposed to volatile anesthetics exhibit higher frequency of chromosomal damage [6]. These findings imply direct carcinogenic effects of inhaled anesthetic agents, making the issue of perioperative tumor progression an even more complex matter.

The Effect of Regional Anesthesia on Cancer Recurrence

In a retrospective study using patient's medical records, Exadaktylos et al. compared recurrence rates in breast cancer patients undergoing mastectomy and axillary clearance/ simple complete mastectomy [7]. One group received a combined general and paravertebral anesthetic while the general anesthesia group received GA and patient controlled analgesia with morphine. Recurrence or metastasis was documented in 3 of 50 patients (6%) in the paravertebral group and in 19 of 79 patients (24%) in the general anesthesia group throughout the follow-up period. A Kaplan-Meier analysis was used to adjust for the varied duration of follow-up for each patient. The study showed that the paravertebral group had longer time to recurrence (P=0.013) Furthermore, in a multivariable analysis adjusting for histologic grade and axillary node involvement, recurrence risk proved significantly less in the paravertebral group [7]. Despite showing interesting and provocative result selection bias and a small sample size are severe limitation of this study. Biki et al. addressed the issue of the effect of epidural anesthesia/analgesia on cancer recurrence after radical prostatectomy [8]. 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. However, the results of study can be difficult to translate considering incomplete information provided by authors in regards to clinical protocol [8]. There is no mention of the quantitative postoperative opioid requirement. It is unclear how many individuals patients dropped off the study, or was not qualified in the first place weakening the validity of this study. Though the evidence provided by Biki et al. 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.

Unfortunately, recent literature review do not support uniformly the idea that regional anesthesia is superior to general anesthesia [9]. Wuethrich et al. 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 [10]. The main strength of this study was the prolonged follow-up time of 14 years. Conclusions are limited since no power or error estimations were done. Also, 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 cyclooxygenase-2, may suppress neoplasm relapse [11]. It is possible that this effect could have influenced the results. In a similar study, Tsui et al. 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 [12]. Among the 99 patients, 22 were lost to follow-up. Biochemical markers of neoplastic 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% confidence interval of 0.6-2.7. Despite randomization, the fact that the study was originally designed for different endpoints renders the study conclusion of the study somewhat limited [12]. Again, the authors call for design of larger prospective trials.

Regional has widely been studied as an alternate and arguably safer anesthetic technique in cancer patients. This is based on the concept of regional anesthesia decreasing or preventing the surgical stress response [13]. Such a stress is perceived as inducing immuno-inhibition or immuno-suppression thus theoretically can contribute to progression of the neoplasm. Regional anesthesia also decreases the need for perioperative opioids, which are believed to have a pro-tumoral effect [14,15]. In addition, studies on bupivacaine suggest that it has direct anti-neoplastic properties via activation of both intrinsic and extrinsic apoptotic pathways in ovarian cancer and the intrinsic pathway in prostate cancer [16]. Still, confounding evidence must be taken into account. Although regional anesthesia can be perceived more favorable than general anesthesia based other studies, there is a predilection in selecting patients for regional anesthesia secondary to their frailty or perceiving patient with widespread disease as better suited for general anesthesia [17]. This significantly biased the results. In fact, once confounders are controlled, studies by Cakmakkaya et al. showed no evidence of improved tumor recurrence and evidence by Cata et al. showed no evidence of prolonged cancer survival1 [7,18].

Mechanism Favoring Type of Anesthesia and Cancer Recurrence

Long-term effect of opioids on neoplasm progression

Post-operatively, opioids are a common choice for pain management in cancer patients. Although the immunosuppressive effect of opioids has been widely documented, some reports argue that opioids' immunomodulatory effects may be beneficial in the context of malignancy [16-18]. The effects of opioids on neoplasia progression likely depend on the extent of their analgesic action, counterbalancing their immunomodulatory effect by decreasing acute pain and attenuating the stress response. Here, we review the confounding evidence for opioid effect on malignancy, which should illustrate the urgency of further studies in humans, comparing patient outcomes with and without opioid use for cancer pain. Intentionally, we will not focus on the direct effects of opioids on immunosuppression since this subject has been reviewed many times [19,20].

Opioids effect on neoplasm survival: Morphine has been the most widely studied opioid with regards to cancer recurrence. It has been found that peripheral opioid receptors help modulate cell proliferation and apoptosis [21,22]. *In vitro* studies have shown the pro-apoptotic action of morphine on cancer cells by different mechanisms including inhibition of NF-κB via nitric oxide [23,24] whereas other studies have shown inhibition of apoptotic processes via p53, a key factor in programmed cell death [25-27]. These findings are somewhat conflicting with data showing an inhibitory effect of morphine tumor cell proliferation *in vitro* [28-31].

Opioids for acute pain: Treatment of postoperative pain with opioids has been shown to reduce cancer recurrence, despite their potential prometastatic effect [32]. Recognizably, 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 [19]. Unfortunately there is a lack of studies evaluating the impact of chronic pain on cancer recurrence due to the obvious limitation of such studies.

Other perioperative considerations

These are outlined in order to acknowledge other ways anesthesiologists can modify neoplasia progression. Although beyond the scope of this review, we hope to use this data to map out comprehensive anesthetic planning to improve outcomes in cancer patients.

Blood transfusion: Theoretically, transfusion-associated immunomodulation (TRIM) is the driving force behind allogeneic blood transfusion related tumor recurrence. This is related to the widely studied immunosuppressive effects of allogeneic blood and the modulation of WBCs in allogenic *vs.* autologous transfusions [33]. A study investigating patients undergoing resection of gastric cancer randomized patients to allogeneic or autologous transfusion. IFNγ, T-helper cell, and T-helper/cytotoxic T-cell ratio were reduced in both groups after operation but the suppression was most profound 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 [34]. Studies on this effect are controversial and remain inconclusive, as current literature does not clearly correlate TRIM with cancer recurrence [33,34].

Perioperative use of β-blockers: It became almost a common practice to use of β-blockers in patients undergoing anesthesia due to the cardiovascular-related issues [35]. However, some studies investigated the effect of pharmacological β-blockade on neoplastic growth. Two studies have shown less distant metastases in patients with prostate and lung cancer [35,36]. In the breast cancer subgroup, evidence strongly suggests a favorable benefit in the use of B-blockers for the reduction of long-term cancer recurrence in particular [37,38]. This was attributed to the attenuation of the natural stress response with β-blockade, resulting in diminished interleukin release during the initial phase of neoplastic seeding. These studies, however, are all retrospective in nature. Stronger blinded randomized trials combined with therapeutic intervention offer better evidence to prompt a change in practice.

The most popular proposed mechanism in which the adrenergic pathway affects tumor progression is via the stress responses, which is correlated with release of adrenergic hormones linked to NK cell suppression, enhanced tumor retention, and perioperative immunosuppression [39,40]. Human studies have shown that patients with depressed NK cell function have higher cancer incidence and metastatic disease after excisional surgery suggesting that this acute, or short-term suppression, can be translated into long-term effect [39,41-43]. Consequently, diminishing the adrenergic pathway, particularly via B-adrenergic inhibition, has been shown to block progression of stress-induced tumors [44,45]. These findings have to be separated from the effect of B-adrenergic agonists itself, which has also been shown to stimulate malignant cell proliferation.

Recently, a paper by Chang et al. 2015 highlighted the importance of chronic stress as a physiological regulator of neural-tumor interactions, and how that microenvironment drives the progression of pancreatic cancer, particularly through B-adrenergic receptor signalling. He has demonstrated that stress on mice, in terms of repeated restraints, changes in cage composition, sound stress, resulted in systemic increase in epinephrine and adrenal gland enlargement as well as pancreatic tumor volume [46]. In fact, majority of pancreatic cancer cell lines and its stromal cells in its vicinity, including macrophages, endothelial cells, and fibroblasts express β-adrenergic receptors. They have even demonstrated that isoproterenol, a non-selective β-adrenergic receptor agonist, increased pancreatic cancer cell proliferation *in vitro*! More importantly, it increased Panc-1 type pancreatic tumor cells' basement membrane invasion in a dose-dependent manner, and these effects were blocked with propranolol, a B-blocker. When exposed to norepinephrine, tumor's expression of matrix metalloproteinases (MMPs), an enzyme that degrades the extracellular matrix, is upregulated. Similar to the upregulation of MMPs as a tumor grows in grade. Inhibiting β-adrenergic signaling to pancreatic cancer cells induced apoptosis by suppressing the Ras/Akt/NFκB signaling pathway [47,48]. Similar findings were also reported in studies of hemangioma, neuroblastoma, melanoma and gastric cancer [49-52]. Chang et al. go as far as to support the use of β-blockers as a possible novel therapeutic intervention, but that claim must be utilized with caution, as recent studies by Wang et al. stated that B2 adrenergic stimulation with norepinephrine has actually attenuated invasion of certain types of breast CA's migration [53]. Thus despite overwhelming evidence that B-adrenergic stress responses is pro-cancerous, there is still need to quantify the exact types of cancers that are amenable to this type of therapy.

Hypothermia: Current literature suggests that hypothermia stimulates a stress response and glucocorticoid release augmenting

immunosuppressive effects. Thus, hypothermia could be mechanistically linked to neoplastic recurrence in a similar fashion as the use of β-blockers. Although further studies in humans are needed, animal studies show that a temperature of 30.8°C suppresses NK cell activity and also suppresses resistance to neoplastic metastasis [54]. Similarly, mild hypothermia has been shown to exacerbate immunosuppression in abdominal surgeries of non-cancer patients [55]. Further studies of could elucidate whether a change in intraoperative body temperature management would provide better patient outcomes after surgical resection of the neoplasm.

How Optimal Management of Anesthesia can Impact Patient Recovery from Neoplasm

How we should modify our anesthetic plan to improve outcomes for cancer patients will continue to be a difficult debate. This debate also touches on the issue of future of our profession in both clinical importance and academic development. As indicated above, multiple studies have attempted to answer this question by looking at specific anesthetics or anesthetic procedure types and their immunomodulatory outcomes. In hopes to answer how we should modify anesthetic plan to diminish cancer recurrence or propagation, one thing is clear- a proper balance has to be established. As written above, not only does the anesthetic type matter, but also the mode in which these anesthetic are implemented, for example whether via general or regional, should be considered in how it translates to cancer outcome. Unfortunately, most studies have been retrospective trials, and these studies are subject to some confounders. Although regional anesthesia seems to be better than general anesthesia as implicated before, cancer patients who were designated to receive general rather than regional anesthesia may have more tumors that needed to be excised, which correlates to the extent of cancer metastasis and so higher cancer severity and poorer outcomes already.

In conclusion, there is still not enough evidence to make a definitive anesthetic plan for cancerous patients to diminish cancer recurrence or propagation. However, some broad statements can be drawn- first, opioids should be avoided except in acute pain, and if an opioid is utilized morphine rather than fentanyl is preferred. Obviously the type of surgery and the length of anesthetic requirements are still going to largely dictate the type of anesthetic use, prospective studies with these variables held constant while comparing morphine versus fentanyl use would be helpful. Second, there is still no significant difference in regional versus general anesthetic modalities found in prospective studies, even though overwhelming retrospective studies have shown otherwise. At this time, the type of anesthetic modality a cancer patient receives should depend on which modality or even modalities will offer the best pain control during and after surgery. And the stresses of pain causing catecholamine release and subsequent cancer progression via the B-adrenergic pathway is much more validated.

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