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Perioperative Interventions During Cancer Surgery: Can Anesthetic and Analgesic Techniques Influence Outcome?

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Abstract Cancer is the second most significant cause of morbidity and mortality worldwide. While surgery is the primary treatment form most cancers, the perioperative period and surgical stress may cause an increased propensity for loco-regional or distant metastasis. There is perhaps a signal, from in vitro, animal model laboratory studies, and retrospective clinical studies, which collectively suggest a possible effect of various anesthetic agents and techniques on tumor metastasis and survival of minimal residual cancer. Prospective randomized control trials are needed in order to truly evaluate any effect anesthesia may have on the metastatic tendency of various tumors.

Keywords Cancer · Anesthesia · Metastasis · Immune modulation · Regional anesthesia · Opioids

Introduction

Cancer remains the second largest cause of morbidity and mortality in the developed world. In many cases surgical resection of the primary solid tumor is the mainstay of treatment; however, it is often the metastasis that poses the greatest risk to life.

As shown in Fig. 1, metastasis is a complex multi-step process involving detachment of malignant cells from the primary tumor mass, invasion into lymphatic or vascular network, and extravasation at the site of metastasis, followed by proliferation at the secondary site.

Despite surgical excision of the primary tumor, there remain invisible tumor deposits (micrometastasis) and inadvertent displacement of tumor cells into the circulation [Circulating Tumor Cells (CTCs)] at the time of surgery which may subsequently develop into clinical metastasis. Whether micrometastasis or CTC become established cancer recurrence or are repelled by the patient's immune system may depend on the balance between conflicting forces active the perioperative period which may facilitate or inhibit cancer cell growth and development.

For almost a decade, there has been a growing research interest whether the effects of various different perioperative drugs, techniques and interventions could influence loco-regional recurrence or metastasis. This review aims to summarize the rationale underpinning for this hypothesis and the current evidence base in this field.

Regional Anesthesia

Although there are ongoing multicenter prospective randomized control trials to evaluate the effects of paravertebral anesthesia on breast cancer (NCT 00418457) and the effects of epidural anesthesia on colorectal cancer (NCT00684229), all current research on the long-term outcomes of regional anesthesia in cancer surgery comes from retrospective human and live animal studies.

There are early animal studies which clearly demonstrate an effect of regional anesthesia in rat cancer models

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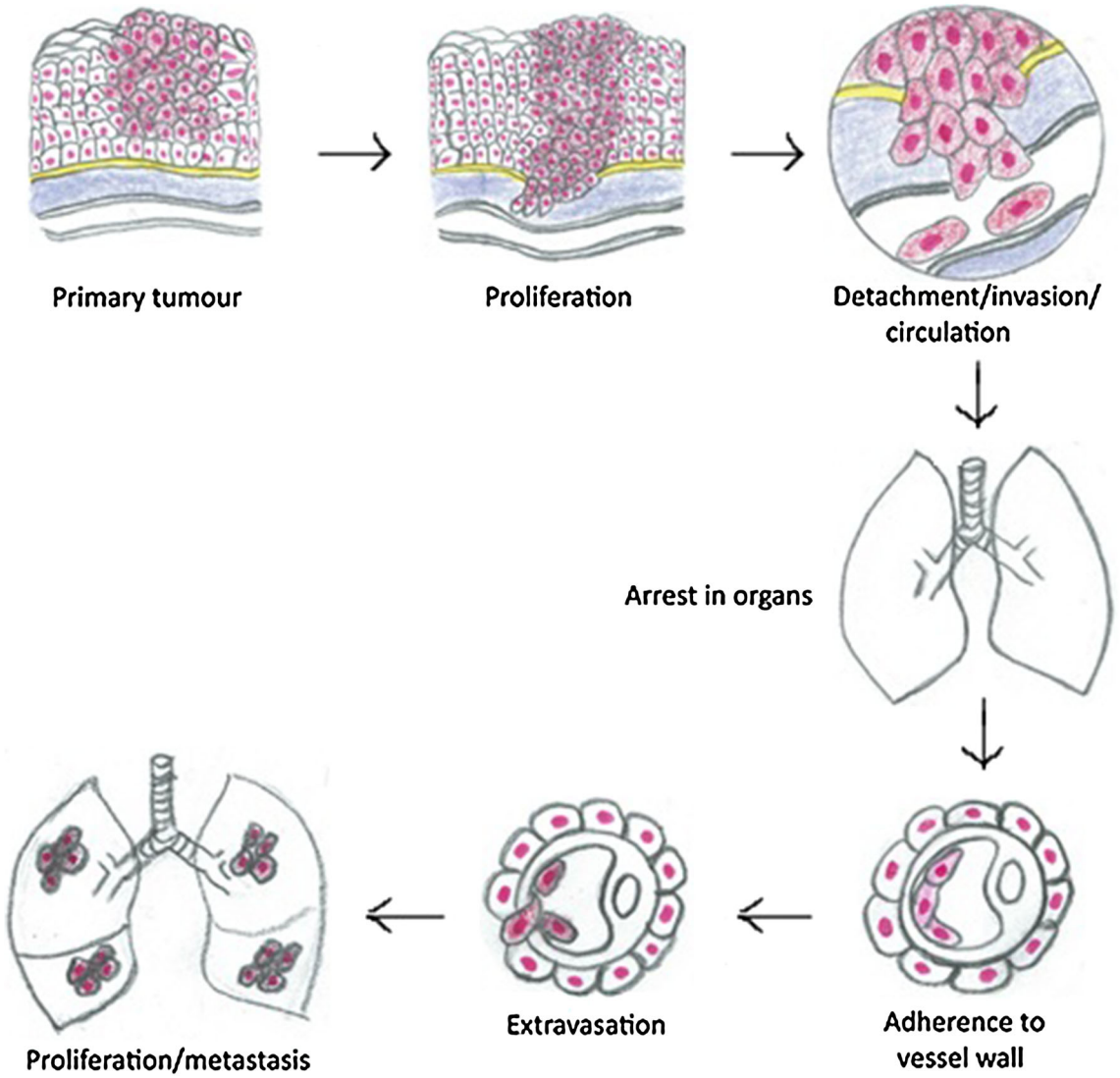

Fig. 1 Metastasis. Simplified schema of the metastasis process. Metastasis is a complex process involving multiple steps including proliferation of the tumor. This is then followed by invasion into the circulation. These circulating cells adhere to the endothelial walls in the target organs and extravasate. Once in the target organ the metastatic cells can then multiply

[1, 12]. Two retrospective human trials looking at the effects of regional anesthesia on metastasis and survival have generated interest in this field. The first, a study by Exadaktylos and colleagues in 2006 [2] compared patients receiving paravertebral anesthesia total intravenous anesthesia (TIVA) with propofol with balanced volatile-based general anesthetic with opioid-based analgesia (GA) for breast cancer surgery. The same group compared patients receiving an epidural and general anesthesia to those who received a balanced general anesthetic and post-operative patient controlled PCA for radical prostatectomy. They found that patients who received general anesthesia with epidural analgesia had a 57 % lower risk of cancer recurrence than patients who had general anesthesia and post-operative opioids [3]. In contrast to these optimistic results, there are other studies which did not find a difference in recurrence or metastasis when regional anesthesia was utilized. One such retrospective study compared recurrence rates of those patients who received an epidural to those who did not for surgery for late stage ovarian malignancy [4]. However, a retrospective study on the influence of epidural anesthesia on surgery for upper gastroenterological malignancies found that there was a different association between epidural anesthesia and esophageal tumors versus gastric tumors and that histological tumor grade is also important in determining cancer outcome. Further, this retrospective study suggested an association between longer duration of epidural exposure and better cancer recurrence rates, suggesting a dose–response like effect of continuous epidural analgesia after cancer surgery [5].

Perioperative epidural analgesia reduces cancer recurrence after gastro-esophageal surgery.

A further retrospective study looking at the effects of regional anesthesia in surgery for colorectal carcinoma found that it did not reduce recurrence overall in those younger than 64 years of age but did find a small difference in those patients above this age [6]. A long-term follow-up analysis of the MASTER trial, the first prospective clinical study in which patients undergoing laparotomy, were randomized to receive GA with either epidural or opioid analgesia found no difference in cancer-free survival between the groups. The median time to recurrence of cancer or death was 2.8 (95 % confidence interval 0.7–8.7) years in the control group and 2.6 (0.7–8.7) years in the epidural group ($P = 0.61$). Recurrence-free survival was similar in both epidural and control groups (hazard ratio 0.95, 95 % confidence interval 0.76–1.17; $P = 0.61$) [7]. Possible confounding factors include an increased requirement for volatile anesthetic in the opioid analgesia group.

There are a number of potential mechanisms by which regional anesthesia may affect the rate of recurrence including reducing or abolishing the neuroendocrine component of the stress response, reduction in requirement for opioids and volatile anesthetics, modulation of the immune system, the direct effect of local anesthetic, and reduced secretion of proangiogenic factors such as VEGF.

There are two components to the perioperative surgical stress response. Firstly, there is the neuroendocrine response, which is responsible for catecholamine release from the adrenal glands and subsequent natural killer cell suppression possibly leading to increased metastatic activity. These effects of the surgical stress response could be blocked by an effective regional anesthesia [8]. The cytokine component of the stress response is not affected by regional techniques but may be attenuated by the administration of cyclooxygenase inhibitors. Regional anesthesia reduces the requirement for opioids and volatile anesthetics by reducing or eliminating both the nociceptor transmission and the neuroendocrine component of the stress response, which may influence the metastatic potential of tumors.

Local anesthetic agents are used to achieve regional anesthesia. It has been shown that intravenous local anesthetics may reduce the rate of cancer metastasis via a variety of mechanisms. It is possible that at least part of the effect seen is due to the systemic absorption of infused local anesthetic into the bloodstream for a systemic effect.

The body's main defense against metastasis is cell-mediated immunity and in particular the natural killer (NK) cells. NK cells are cytotoxic lymphocytes that recognize tumor cells without sensitization and can mount an immune response [9]. Immune cell infiltration into human tumor stroma appears to be particularly important and may regulate anti-tumor immune resistance and be an important harbinger of prognosis in certain types of cancer [10].

Experimental data from an inoculation model of breast cancer in live animal models suggest that regional anesthesia attenuates perioperative immune impairment, particularly by preserving natural killer (NK) cell function [11]. Data from another animal model suggests that regional anesthesia modifies the T lymphocyte balance peri-operatively, in a manner conducive to resisting hepatic tumor development [12]. Serum drawn from women undergoing surgery for breast cancer who were randomized to receive a paravertebral block and TIVA anesthetic technique led to greater human donor NK cell cytotoxicity in vitro compared with serum from women who received GA [13•]. A further study by the same group found that the serum from patients randomized to receive the balanced general anesthetic had decreased apoptotic rates in ER-negative breast cancer [14]. Desmond and colleagues examined breast tissue excised from patients on the NCT00418457 trial, looking at the differential effect of paravertebral regional anesthesia with TIVA vs GA (with volatile) and morphine analgesia for breast cancer excision on metastasis. The tissue of 28 patients was stained for CD56 (NK cells), CD4 (T helper cells), CD8 (T suppressor cells), and CD68 (macrophages). Examination of the stained slides revealed a significantly lower NK cell population in the group that received the regional and TIVA. There were no differences in CD68 or CD8 populations [15•].

There are a number of essential biological functions which are essential for cancer cells to survive, thrive and metastasize. These include the ability to proliferate, migrate, invasion into adjacent tissue and induce angiogenesis, the process by which tumor tissue acquires a blood supply. A number of studies have focused on the direct effect of regional anesthesia on angiogenesis. Angiogenesis is stimulated partly by synthesis and secretion of vascular endothelial growth factor (VEGF). There is some debate over whether or not regional anesthesia can reduce angiogenesis. There are three prominent prospective trials investigating the effect of regional anesthesia on the post-operative levels of factors promoting angiogenesis. The first of these studies compares the levels of VEGF and prostaglandin E2 (PGE2) [16] in 30 patients undergoing breast cancer surgery. Patients were randomized into two groups with one group receiving a paravertebral block while the other group was managed with morphine analgesia, both groups received a general anesthetic with sevoflurane and nitrous oxide. Venous blood samples were taken preoperatively and at 4 and 24 h post-operatively and tested for VEGF and PGE2. No difference was demonstrated between the groups.

In a study by the same group [16], 40 patients undergoing surgery for breast cancer were randomized to get either a paravertebral regional block with TIVA while the

second group received a balanced sevoflurane maintained GA plus morphine analgesia as part of the international prospective randomized control trial NCT00418457. The results showed a mean post-operative change in VEGF concentrations among GA patients of 733 versus 27 pg/ml for paravertebral and TIVA patients [difference, 706 (97.5 % CI 280–1130) pg/ml, $P = 0.001$]. In contrast, the mean post-operative change in transforming growth factor β concentration among GA patients was −163 versus 146 pg/ml for paravertebral and TIVA patients [difference 309 (97.5 % CI −474 to −143) pg/ml, $P = 0.005$] [17]. Both VEGF and transforming growth factor β are important for the proliferation of tumor cells and angiogenesis. This study demonstrates that paravertebral anesthesia and TIVA for breast cancer reduces the levels of these factors post-operatively when compared to a balanced general anesthetic with morphine analgesia. The effect on metastasis and disease-free survival will not be known till completion of the study.

The third prospective study investigating the effect of regional anesthesia on VEGF levels in cancer surgery looked at the effect of an epidural regional technique for colorectal cancer. This study involved randomization of 40 patients into two equal groups, the first of which received a general anesthetic with a volatile-based GA and morphine analgesia, the other group received an epidural and TIVA with propofol. Significantly, patients who received an epidural and TIVA showed decreases in VEGF [526 (261) vs 834 (304) pg/ml, $P = 0.001$], TGF-β ($P = 0.027$) 24 h after surgery compared with patients subjected to GA. These studies collectively demonstrate a potential benefit from using the combined approach of TIVA and regional anesthesia for cancer anesthesia. The combined approach of TIVA and regional anesthesia results in lower detectable levels of proangiogenic factors which may result in a lower metastatic rate. To translate these in vitro findings into clinical results further follow-up is required.

Volatile Anesthetic Agents

Investigation of the effects of volatile anesthetics on cancer biology in human subjects is difficult since in any tumor surgery there are likely to be many confounding factors, the effects of which cannot be separated from the effects of the volatile anesthetic. It is for this reason that most of the research in this area comes from mouse models or cell culture studies. In comparison to regional anesthetics, retrospective analysis indicates that volatile anesthetics have a less favorable outcome in both melanoma [18] and radical prostate cancer surgery [3].

Almost forty years ago it was shown that anesthetics such as halothane and nitrous oxide accelerate metastasis in murine models of melanoma and lung cancer [19]. More recent studies indicate that volatile anesthetics may up-regulate cellular signaling pathways including the hypoxia inducible factor 1-α (HIF-1α) pathway [20]. HIF-1α is a transcription factor involved with many aspects of tumor cell behavior including angiogenesis, proliferation, and invasion [21], hence high levels of HIF-1α can be linked to a more aggressive tumor [22]. HIF-1α is also linked to a relative radiotherapy and chemotherapy resistance [23]. The effect of the volatile agents on metastasis appears to be dose and time dependent [24]. It is unclear how these findings will translate to humans especially when we consider the fact that all research in this area to date has been carried out under normoxic conditions (21 % O_2), however, many tumor environments are relatively hypoxic which has been shown to alter the expression of HIF-1α. On the contrary, there is data to suggest that sevoflurane and desflurane may actually decrease migration of colon cancer cells by reducing the production of matrix-metalloproteinase by neutrophils [25]. Also sevoflurane may increase the migration of these tumor cells, however, the research was carried out in an oxygen rich atmosphere and the difference in the results may be directly attributable to this [17].

Xenon is a noble gas with many favorable anesthetic properties. Sadly it has not achieved widespread acceptance due to its exorbitant production price. It is currently in clinical use only in Russia and Germany. Research into the effects of clinical concentrations of xenon on human breast cancer cells demonstrated a decrease in migration but no change in cell viability [26]. This effect to decrease cell migration was inhibited by the administration of glycine indicating involvement of the N-methyl-D-aspartate receptor.

Nitrous oxide has many potential biological effects including depression of neutrophil chemotaxis [27] and inhibition of formation of haematopoietic stem cells. This effect on the immune system could plausibly be thought to reduce the cancer immunosurveillance and hence increase the risk of metastasis. In keeping with this, melanoma and lung cancer mouse model experimentation revealed a dramatic increase in the rate of metastasis when nitrous oxide was included in the anesthetic [19]. These findings do not appear to translate well for human colorectal cancer. In a study designed to look at differential rates of post-operative infection after colectomy in which one group were given 65 % nitrous oxide in oxygen and the other group were given 65 % nitrogen in an oxygen mixture, there was no difference in the rates of metastasis in the groups after a follow-up period of 4–8 years [28].

Taken together, to date all our knowledge about the effects of the volatile anesthetics and anesthetic gases in cancer cell biology comes from animal and cell culture

experiments. In general there appears to be a signal that the volatile anesthetics may increase the tendency for metastasis but it is unclear at the current time if these results can be reliably extrapolated to humans.

Intravenous Anesthetic Agents and TIVA

Propofol (2,6 di-isopropyl phenol) is the most commonly used intravenous anesthetic and is used for both induction and maintenance of anesthesia. Propofol has many diverse actions in addition to its anesthetic actions [29]. Its effects have been studied in many different cancer types including cholangiocarcinoma, lung cancer, and breast cancer, using in vitro cell culture studies.

Zhang et al. [30] studied the effect of propofol on the proliferation, apoptosis, and invasion of cholangiocarcinoma cell cultures and found that proliferation and invasion of the cancer was increased and apoptosis was decreased in a dose-dependent manner with increasing doses of propofol perhaps by up-regulating Nrf2 which is a transcription factor activated by stress.

Wang et al. [31] studied the effect of propofol on chemosensitivity and invasion of both paclitaxel sensitive and resistant ovarian cancer cells. In this study, the results suggest that the administration of propofol to ovarian cancer cell cultures reduces the invasiveness of the cells and also increases their sensitivity to paclitaxel, due to downregulation of the transcription factor slug [32]. These apparently beneficial effects were also seen in similar in vitro studies in breast cancer cells [33].

In vitro studies on both estrogen receptor positive and negative breast cancer cells found that propofol reduced expression of the Neuroepithelial Cell Transforming Gene 1 (NET1) which in turn reduced the migration of these breast cancer cells [34]. The NET1 gene expression was previously studied in adenocarcinoma cells and was found to be involved with the promotion of migration.

While the in vitro effects of propofol on cell culture studies on migration and invasion are inconsistent, the apparent beneficial effects of propofol on cancer cell biology may be relevant in the presence of an effective regional block. However, this hypothesis will require testing in a prospective, randomized trial.

Opioids

Opioids have long been the mainstay of pain management especially in the perioperative period. The effects of opioids on the rate of metastasis of non-small-cell lung cancer, melanoma, breast cancer, colon cancer, and prostate cancer have been investigated mainly in animal models. The mechanism by which opioids effect the rate of metastasis appear to be multifactorial and includes immunosuppression and direct effects on the tumor cell which may be facilitated by an increase in the tumor cell expression of the μ-opioid receptor and possibly an increase in concentrations of endogenous opioids.

Many of the anesthetic and analgesic agents that alter the invasiveness of tumor cells appear to do so, at least in part, by immunomodulation and in particular, natural killer cell modulation. The opioids are no exception, with experimental and human retrospective research pointing towards a decrease in NK cell migration and activity as well as a shift from a beneficial pro-inflammatory state to an detrimental anti-inflammatory state via a change in interleukin secretion with opioid administration [35–37]. There is also evidence to suggest that not all opioids have a similar effect on the immune system. Tramadol which has serotonin and norepinephrine reuptake inhibitor activity along with its weak opioid activity has the opposite effect to morphine in that it stimulates NK cell activity both in rodents and humans [38–40].

There is evidence to suggest that morphine may induce angiogenesis. Gupta and colleagues noted an increase in vascularity in breast cancer xenografts injected into nude mice when the mice were treated with morphine, an effect that is inhibited by naloxone [41]. In laboratory studies of human dermal and pulmonary endothelial cells, Singleton et al. demonstrated that both morphine and an experimental selective mu-opioid receptor (MOR) agonist both stimulate endothelial cell migration and proliferation via a pathway involving the reciprocal transactivation of the VEGF receptor, a process that can also be inhibited by MOR antagonism with methylnaltrexone [42]. This observed increase in angiogenesis may occur via a mechanism involving Src signaling factor activation and the transactivation of the vascular endothelial derived growth factor receptor [43] or via upregulation of the Cyclooxygenase-2 enzyme and a subsequent increase in prostaglandin E_2 [44]. The proposed tumor-protective effects of non-steroidal anti-inflammatories are believed to occur via inhibition of the COX-2 pathway while the protective effects of local anesthetics may work via the inhibition of Src phosphorylation.

Studies have demonstrated that the MOR expression is also altered in tumor cells and there is an increase in cell surface expression in some tumors. Singleton et al. reported a two fold increase in cell surface MOR in the cells of NSCLC [45•]. Zylla et al. [46] examined the MOR expression and opioid requirement in 113 patients with stage 4 prostate cancer and found that both MOR expression and opioid requirement were independently associated with inferior progression-free survival and overall survival. This study also found that when the MOR expression and

opioid requirement were included in the multivariate model, the significance of other known prognostic variables diminished considerably. It was also found that injecting Lewis lung cancer cells into nude MOR knockout mice did not result in the growth of a tumor while it almost invariably did in the case of normal mice [47]. The in vitro work of Ecimovic et al. [48] demonstrated that morphine increases the migration of both estrogen positive and negative breast cancer cells in a dose-dependent way by 17–27 %. Further investigation revealed that the NET1 gene expression was also increased in a dose-dependent way with morphine administration and when this gene was knocked out, it was found that there was no reaction of the cells to the opioid. It was also hypothesized that is the delta opioid and the atypical nociception opioid receptors involved rather than MOR in estrogen receptor negative and estrogen receptor positive cells. The latest research on the effect of morphine on breast cancer cells in mice suggests that MOR expression is not increased in small tumors but is greatly increased in large tumors, a process that is believed to be due to cytokine and growth factors excreted as tumors grows. This is all particularly relevant when we consider the fact that MOR can also be activated by endogenous opioids and studies on breast cancer and human melanoma demonstrate an increased blood level of endogenous opioid in these patients [49, 50].

The pro-metastatic effects of opioids appear to be peripherally rather than centrally mediated. This is supported by the observational study of palliative care patients demonstrating that patients receiving intrathecal opioids exhibited increased survival compared with those receiving comprehensive medical management [51].

All things considered it would appear that despite some contradiction in the published research, opioids may indeed have a tumor enhancing effect in the animal models and in vitro models studied. The effect appears to be multifactorial and includes an increase in the MOR concentration, increase in angiogenesis and an increase in tumor bulk. Although there is much research in this area, we are still lacking concrete evidence of an effect in humans.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Prostaglandins are hormone-like lipid metabolites produced by the action of cyclooxygenase on fatty acids. Prostaglandins have many physiological and pathophysiological actions. There are 3 known forms of the cyclooxygenase enzymes which are coded for by different genes. COX-1 is constitutively expressed in cells while COX-2 is an inducible form and COX-3 is mainly expressed in the central nervous system. There is a significant body of evidence suggesting that COX-derived prostaglandins contribute to tumorigenesis [52] and in particular prostaglandin E2 is implicated [53].

The role of COX-2 and prostaglandins in tumorigenesis and invasion were first suspected after epidemiological evidence demonstrated that regular intake of aspirin reduced the risk of colorectal cancer [54]. A further study involving the use of the NSAID sulindac in patients with familial adenomatous polyposis demonstrated a marked reduction in polyp number and size after a year, a change that was reversed by discontinuation of the drug [55]. Then it was discovered that COX-2 is overexpressed in colorectal carcinomas [56]. In 76 patients with colorectal carcinomas, COX-2 was overexpressed in both the tumor epithelial cells and also in the endothelium of the tumor vessels. These investigators correlated the COX-2 expression with Dukes staging, local tumor spread and 5-year survival and found that higher COX-2 expression correlated well with more advanced Dukes staging, and a reduced survival rate but failed to show a correlation with local tumor spread [57]. Rizzo et al. demonstrated that colorectal carcinoma cells with COX-2 overexpression tended to metastasize more frequently than those with a less pronounced expression [58]. In contrast to these data, the phase III randomized trial of rofecoxib in the adjuvant setting of colorectal cancer failed to demonstrate a survival advantage in the group receiving the rofecoxib, and failed to show a correlation with overall prognosis [59].

Up to 40–50 % of invasive breast carcinomas overexpress COX-2 [60, 61]. COX-2 expression is highest in ductal carcinomas in situ [62]. A study examining 248 cases of breast cancer demonstrated a more dramatic increase in COX-2 expression in those cells that were hormone receptor negative and human epidermal growth factor positive and also correlated well with activation of the oncogene Atk and with a decreased survival [63]. It would also appear that silencing the COX-2 in breast cancer cells resulted in a profound decrease in metastasis and tumor onset in vitro [64]. The retrospective study of Retsky et al. [65] supported these findings by demonstrating a fivefold reduction in relapses within the first 18 months in patients administered ketorolac, a widely used NSAID.

Lung cancer also appears to be tightly linked to COX-2 expression. Investigators have observed COX-2 overexpression in 70–90 % of lung adenocarcinomas [66]. The significance of this COX-2 overexpression has been intensely debated with a number of studies demonstrating a significant correlation between elevated COX-2 levels and poor prognosis [67] and more aggressive disease [68] in non-small-cell lung cancer. Both non-selective [69, 70] and selective COX-2 [71] inhibition have been associated with a reduced risk of developing NSCLC of between 36 and 63 %. There seems to be an indication for randomized

controlled trials evaluating the effect of NSAIDs especially COX2 inhibitors in preventing cancer recurrence after primary excisional surgery.

Oxygen Supplementation

Oxygen supplementation is commonly used in the perioperative period. There is experimental evidence to suggest that a high fraction of inspired oxygen in the presence of damaged DNA may induce cell division via a mechanism involving free radical or reactive oxygen species generation.

The PROXI trial was originally set up in Denmark in 2006 to look at the effect of high inspired oxygen concentration on wound healing in patients undergoing laparotomy. The study involved 1386 patients who underwent elective or emergency laparotomy and were randomized to get either 30 or 80 % oxygen from the start on anesthesia till 2 h after surgery. These patients were followed up 4 years post-op. The findings were that a high FiO_2 increases surgical site infection. A post hoc analysis of the data found that although rate of new cancer diagnosis was similar in both groups, the average time to diagnosis of cancer was median 100 days shorter in the 80 % oxygen group.

While the sample size is sufficient to provide statistically significant results, the data does not allow for histology-specific analysis of the groups, nor does it allow us to look at the effects of hyperoxia on the immune cells and growth factor production. From laboratory data, it is known that an increase in tissue oxygen tension causes free radical formation and also increases growth factors such as erythropoietin. However, prospective randomized, cancer histology-specific clinical trials are needed before we can definitively state that a high inspired oxygen fraction has the potential to encourage cancer metastasis or growth.

Intravenous Local Anesthetic Agents

Local anesthetic agents work by inhibiting sodium flux through voltage-gated sodium channels (VGSC) on nociceptive neurons and on other cells, including tumor cells. There is also evidence to suggest that local anesthetics have an anti-inflammatory action, which does not rely on their action at VGSC. The majority of the work on the action of local anesthetics on tumor cells has been carried out at the cellular and genetic levels with very little work being carried out in vivo.

Histological analysis of cells from breast cancer, lung cancer (small cell, non-small cell, and mesothelioma), cervical cancer, ovarian cancer, colon cancer, and prostate cancer reveal increased VGSC expression [72] which appears to be coupled with a down regulation of voltage-gated potassium channels [73] thereby making the cells more excitable as sodium can enter with greater ease while potassium can't efflux. Voltage-gated potassium channels have been linked to an increased apoptosis and growth [74].

As is displayed in Fig. 2 there are many possible mechanisms that may either act synergistically or independently to explain the increased patient survival seen with intravenous anesthetics. The first mechanism displayed in panel A involves the analgesic effects of local anesthetics thus reducing the opioid requirement, which as already mentioned, has multiple potential effect to increase post-operative survival.

The second potential mechanism involves modulation of the cell excitability hypothesis of metastasis. This hypothesis states that strongly metastatic cells have hyper excitable membranes and it is this excitability that confers their metastatic ability [75•]. In vitro experimentation using a whole cell patch clamp technique demonstrated that strongly metastatic cells were significantly depolarized, this phenomenon was not observed in tumor cells with weak metastatic potential [76, 77]. It has also been noted that the behavior of the strongly metastatic tumor cells is dramatically altered by tetrodotoxin, a voltage-gated sodium channel blocker. In vitro experimentation on prostate cancer cells demonstrates that, at least in this type of cancer cell, voltage-gated sodium channel activity promotes cellular motility and a range of other metastatic cell behaviors in prostate cancer. The exact mechanism by which the depolarization of these cells causes an increase in the metastatic ability of these cells is unknown but it may include downstream signaling via adenylate cyclase or calcium influx into the cytoplasm. Furthermore, it would seem that increased sodium influx acts via a positive feedback mechanism to increase transcription of VGSC [78]. In vitro studies of different human cancer cell lines have discovered that different cancers express different subtypes of VGSC. In breast and colon cancers it is the Nav 1.5 that is predominant [77, 79] while it is the Nav 1.7 VGSC that predominates in prostrate and non-small-cell lung cancers [80, 81] and Nav 1.6 predominates in breast cancer. Interestingly enough, it is the neonatal splice variant that is expressed in these cells [82].

The third possible mechanism involves demethylation of deoxyribonucleic acid (DNA). Methylation of DNA is of importance in the control of gene expression with highly methylated genes being silenced. Methylation of tumor suppressor and onco genes is therefore of importance in the suppression of tumor activity and the control of the tumor suppressor genes [83]. This fact has been exploited in the development of new pharmaceutical agents designed to demethylate tumor DNA [84]. In vitro experimentation on

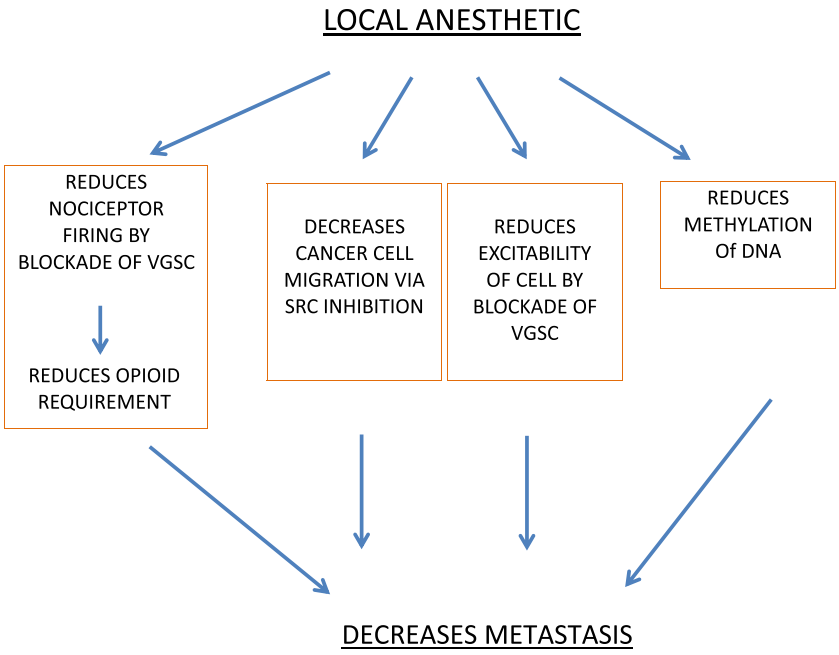

Fig. 2 The processes by which local anesthetics may reduce metastasis. Research indicates that local anesthetics can have multiple effects at the cellular level. The primary effect is to reduce nociceptor firing, thereby reducing the requirement for opioids and volatile anesthetic agents. Local anesthetics may reduce the expression of the SRC oncogene and also decrease methylation of DNA, thereby reducing the metastatic potential of cancer cells. Local anesthetics may also alter the excitability of tumor cells and so may alter gene expression or behavioral aspects of tumor cells

both estrogen positive and negative cells has demonstrated demethylation of DNA at clinically relevant concentrations of lidocaine and ropivicaine [85]. It also appears that the potency of lidocaine is far greater than that of other local anesthetic agents. The proposed mechanism by which this demethylation occurs appears to involve inhibition of DNA methyl transferase [86].

Local anesthetic agents may also have anti-inflammatory actions via a non-voltage-gated sodium channel mechanism [87]. Although the exact mechanism is not fully elucidated, it appears to involve the Src proto-oncogene. Local anesthetics appear to down regulate Src autophosphorylation, either directly or by interfering with the inflammatory mediators such as tumor necrosis factor α (TNF-α) [88]. Src activation is known to play a key roll in cancer metastasis and leads to an increase in vascular permeability [89], increased expression of Intercellular Adhesion Molecule 1 [90], and is involved with the epithelial to mesenchymal transformation and extravasation of tumor cells [91, 92]. In vitro investigation of the effects of local anesthetics on the expression of Src in cultures of small-cell lung cancer revealed a significant decrease in Src phosphorylation with both ropivacaine and lidocaine but not with the ester-linked local anesthetic chloroprocaine [20, 93], indicating that the mechanism of action is not based upon the blockade of voltage-gated sodium channels.

While there are many in vitro studies demonstrating a favorable effect of local anesthetic agents on cell cultures, there remains an absence of prospective trials investigating its effect in vivo. Retrospective clinical studies using nerve blocks have, in some cases shown an association between their use and metastatic reduction, however, causality cannot be demonstrated in the absence of prospective trials.

Blood Product Transfusion

Significant blood loss may necessitate transfusion of blood products during cancer surgery. A Cochrane review of 36 studies established a statistically significant association between transfusion and early recurrence of colorectal cancer. The volume of infusion also appears to be important [94]. In their study of the effect of transfusion of blood products in stage II colorectal carcinoma on outcome, Meng et al. [95]. demonstrated a significant difference in mortality, local recurrence and distant metastasis between those patients who were transfused with more than three units and those who did not receive a transfusion. The observed difference is merely an association between transfusion and increased cancer risk may be due to either immunomodulation or surgical technique. A recent double-blind comparison of $n = 198$ patients with cancer, who were randomized to receive either a liberal blood transfusion regimen (transfusion given if Hb < 9 g/dl) or a restrictive blood transfusion regimen (transfusion only if Hb < 7 g/dl) found that a composite of morbidity and mortality was reduced from 36 to 20 % in the liberal transfusion group, $P = 0.01$ [96].

While this data suggests a benefit to liberal transfusion practice in post-operative cancer patients, both anemia and transfusion are each associated with adverse outcomes. Again, prospective randomized controlled trials are indicated to determine whether this link is truly causal.

Table 1 Ongoing research investigating the effects of anesthetic agents on immune cell function and metastasis

NCT number	Type of cancer	Arms of investigation	Principal investigator
2089178	Breast cancer	TIVA vs inhalational anesthesia	Bon Nyeo Koo
418457	Breast cancer	Regional plus TIVA vs general anesthesia + opioids	Donal J Buggy
2005770	Breast cancer	TIVA vs inhalational anesthesia	Beatrice Beck Schimmer
1916317	Breast cancer	Peritumoral local anesthesia vs no peritumoral local anesthesia	Rajendra A Badwe
684229	Colon cancer	Regional vs general anesthesia	Andrea Kurz
2326727	Colon cancer	Epidural anesthesia vs no epidural anesthesia	Leonid Reytman
2335151	Pancreatic cancer	TIVA vs inhalational anesthesia	Beatrice Beck Schimmer
1854021	Tongue cancer	TIVA vs combined intravenous-inhalational anesthesia vs inhalational anesthesia	Tiejun Zhang
1588847	Malignant melanoma	Regional vs general anesthesia	Hugo K Van Aken

Many of these studies will not be complete until between 2017 and 2019

Glucocorticoids

Perioperative dexamethasone reduces pain, nausea, and vomiting but also acts as an immunosuppressant with a particularly pronounced effect on natural killer cells [97]. It is therefore possible that glucocorticoids can increase the tendency for micrometastasis to develop. The question remains as to whether the typical doses used in the perioperative period (4–10 mg) can have an effect on the growth of tumor cells. The limited research in this area appears contradictory. In their retrospective analysis of the effects of a single perioperative dose of dexamethasone on the recurrence rate of ovarian cancer in 260 patients, Gildasio et al. [98] found no difference between the group who received dexamethasone and those that did not with a mean follow-up time of 18 months. In contrast Sing et al. [99•] reported that there was a significantly higher rate of metastasis in the colectomy patients that received dexamethasone dose of 8 mg peri-operatively compared to those who received a placebo (6 compared with 1, $P = 0.04$).

Dexamethasone has been shown to reduce the stress response to surgery [100] which may be immunosuppressive. Hence the immunosuppressive actions of dexamethasone may be balanced by its beneficial action on the stress response. It is plausible that the effect of dexamethasone may depend on the ratio of the effect of dexamethasone on the stress response to the direct immunosuppressive effect.

Conclusion

The perioperative period of cancer surgery is a crucial time for the establishment of metastasis. Over the past decade, there has been extensive investigation of the potential effects perioperative factors and pharmaceuticals on the post-surgical outcome of the malignancy. To date most of the evidence comes from retrospective studies, which are limited and open to bias. There are however a handful of prospective trials ongoing investigating the effects of regional and total intravenous anesthesia with propofol on the recurrence or metastasis after primary cancer surgery (Table 1). The results of these studies may answer if the signal in animal models and in vitro studies, and retrospective clinical studies can be confirmed in clinical practice.

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Compliance with Ethics Guidelines

Conflict of Interest Kirk J. Levins declares that he has no conflict of interest. Donal J. Buggy is supported by an unrestricted research grant from Air Liquide, and is also a member of the Editorial Board of the *British Journal of Anaesthesia*.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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