Current Anesthesiology Reports (2018) 8:411–425
https://doi.org/10.1007/s40140-018-0299-9

CANCER ANESTHESIA (B RIEDEL AND V GOTTUMUKKALA, SECTION EDITORS)

The Effect of Anaesthetic and Analgesic Technique on Oncological Outcomes

Aislinn Sherwin[1] · Donal J. Buggy[1]

Published online: 30 October 2018

Abstract

Purpose of Review The purpose of this review is to provide an examination of the recent literature relating to anaesthesia and analgesia for cancer surgery and their potential effects on cancer recurrence and metastasis.

Recent Findings Opioids continue to have mixed results in terms of their long-term effects on cancer outcomes. While laboratory evidence suggests alterations in immune responses and pro-tumourigenic effects via opioid receptors on cancer cells, clinical evidence is lacking. Regional anaesthesia has the ability to regulate surgical stress response, but retrospective studies provide conflicting results. However, lidocaine appears to have protective functions against cancer and anti-inflammatory properties making it a potentially useful agent perioperatively. An association also exists between the use of non-steroidal anti-inflammatory agents and improved perioperative outcomes; however, prospective clinical studies are required to provide more robust data in this area. Inhalational agents appear to confer increased risk of cancer recurrence in comparison to total intravenous anaesthesia (TIVA). A recent large retrospective trial and in vivo and in vitro evidence point to a beneficial effect of TIVA versus volatiles that should be fully investigated.

Summary Retrospective analysis provides tenuous links between the techniques used perioperatively and potential cancer recurrence and metastasis. In vitro and in vivo animal studies have furthered research in the area, particularly providing mechanisms on how commonly used agents can affect patient outcomes. However, large prospective randomised control trials are required in this area to further the research on anaesthesia and its effects on cancer recurrence and metastasis.

Keywords Anaesthesia · Cancer · Recurrence · Metastasis · Opioids · Regional anaesthesia · Amide local anaesthetics · Non-steroidal anti-inflammatories · Volatile agents · Total intravenous anaesthesia · Propofol

Introduction

Cancer is the fastest growing cause of death in the developed world. In Europe, it is estimated that 3.9 million people will be diagnosed with cancer, while 1.9 million people will die from the disease in 2018 alone [1]. Globally, cancer caused nearly 9 million deaths in 2015 and was second only to cardiovascular disease [2]. While mortality in cancer has been reduced in high income countries, it is expected that its incidence will continue to increase, especially in developing countries [2]. Breast, colorectal, lung and prostate cancers are by far the most common in terms of occurrence while lung, colorectal, breast and pancreatic cancer were the most frequent causes of death [1].

Approximately 60% of patients have surgery as part of the treatment for their cancer, either with curative or palliative intent [3]. Anaesthesia for tumour removal surgery is therefore commonplace in the management of these patients. In 2006, a retrospective analysis of women who underwent breast tumour surgery with paravertebral regional anaesthesia or morphine analgesia suggested an association between the use of paravertebral regional anaesthesia and improved recurrence-free survival time. This work re-ignited the hypothesis that anaesthesia and analgesia factors perioperatively during cancer excision surgery could influence recurrence or metastasis [4]. A consensus statement published in 2014 highlighted the need for increased research in this area [5]. A number of studies have been carried out in the intervening years; however,

This article is part of the Topical Collection on *Cancer Anesthesia*

✉ Aislinn Sherwin
aislinn.sherwin@gmail.com

[1] Mater University Hospital, School of Medicine, University College Dublin, Dublin, Ireland

difficulty remains in conducting large multi-centre randomised control trials to authenticate the data. Up to this point, large retrospective trials have delivered equivocal results and small-scale in vitro studies are yet to be replicated in large prospective clinical studies. The heterogeneity of the population involved, in terms of age, sex, patient comorbidity, tumour stage and type, cancer therapies are all confounding factors.

Our objective is to review and summarise the current literature around anaesthesia and analgesic technique and cancer outcome, in addition to suggested effects of commonly used agents on cancer cell biology.

The PubMed, EMBASE and MedLine Databases were searched for all articles up to September 2018 that related to the following terms: 'anesthesia AND metastasis', 'anesthetic agents AND cancer', 'anesthesia AND cancer recurrence', 'general anesthesia AND cancer recurrence'. All primary sources were retrieved and reviewed by the authors for inclusion.

Surgery and Metastasis

Surgery has a number of directly pro-metastatic effects. Spread of tumour cells into the circulation, the suppression of immune responses and the promotion of proliferative and invasive capabilities of tumour cells can all be responsible for increasing the risk of metastasis [6]. Surgical methods aimed at reducing tumour spillage into the circulation include the use of minimal handling techniques, wound edge protectors, 'en bloc' resection and proximal vascular ligation [7].

The Epithelial-Mesenchymal Transition (EMT) program is a developmental cell-biological program that promotes the properties of cells to allow invasion and metastasis [8•]. Even before surgery and in early stages of tumour development, cells can be activated using the EMT program, and potentially able to disseminate and form distant metastases [9]. Success in metastasis can be governed by the conditions encountered during the cells' transit from the primary tumour site and the surrounding climate during attempts at colonisation [9].

Surgery, even when the patient is unconscious under general anaesthesia, will activate a systemic stress response to promote wound healing and recovery post-operatively. This stress response includes both neuroendocrine and inflammatory elements. When activated, it results in release of many circulating mediators including growth factors, catecholamines, prostaglandins and increased levels of activated immune cells. Both catecholamines and prostaglandins can have direct effects on malignant tissue and activation of specific receptors, e.g. COX-2 [10], β_2-adrenergic receptor [11], and μ-opioid receptors [12] which can lead to promotion of the metastatic potential of tumour tissue [13].

Hypoxia is involved in triggering key processes involved in tumour growth, e.g. angiogenesis [14]. Inadequate blood supply is common in solid tumours and cells can adapt to low oxygen tension conditions [15]. Cell survival is ensured by the activation of a number of key pathways [15]. One of these key pathways is controlled by a transcription factor which is involved in the promotion of angiogenesis, cell proliferation and metastasis—the hypoxia-inducible factor-1 alpha (HIF-1α) pathway [16]. High levels of HIF-1α have been associated with poor prognosis in clinical studies in a variety of solid tumours [17]. Recently, research interest has focussed on the development of HIF-1α specific inhibitors as a potential target for cancer treatment [15].

Surgical manipulation of the tumour can cause release of metastatic cells (circulating tumour cells) or 'tumour emboli' into the circulation and even with clear resected margins, minimal residual disease may remain at the surgical site [18]. Cell-mediated immunity in the prevention of metastatic spread of cancer involves both natural killer (NK) and cytotoxic T lymphocytes [13]. Natural killer cells are primarily programmed to detect and destroy circulating tumour cells and micrometastases [17] and are of key importance, particularly in the perioperative phase. Lower levels of NK cell activity have been associated with higher rates of distant metastases [19]. Clinical studies have shown reductions in number and function of NK cells post-operatively [20], implicating a potential role of anaesthesia technique in attenuating immune response.

Surgery, while often performed for curative intent, inadvertently increases factors related to metastatic and loco-regional recurrence. Improvements in surgical technique and perioperative factors may impact positively on the outcomes of patients undergoing surgical resection of malignant disease.

Opioids

Opioids are an integral component of analgesic treatment in the perioperative period. Interest in the long-term effects of perioperative opioid use stems from retrospective trials and laboratory-based studies suggesting an increase in cancer progression and recurrence associated with their usage [21].

Opioids can affect cancer growth by modulating host immunity and stimulating tumour growth by encouraging angiogenesis [22]. Opioids have effects on both cell-mediated and humoral immunity [23]. Mononuclear phagocytes and lymphocytes can express opioid receptors, e.g. μ-opioid receptors, which are coupled to signal transduction mechanisms [24]. Toll-like receptors (TLR), including toll-like receptor 4 (TLR4), are involved in innate immune system activation process, recognising microbes or ligands of both exogenous and endogenous sources [24]. It is proposed that opioids may have some effect on TLRs, directly

affecting immune cells [22]. In a murine model using macrophage cells exposed to morphine, morphine was demonstrated to reduce both TLR4 levels and protein levels, potentially by activation of the μ-opioid receptor [24]. On the other hand, new clinical-translational data suggests that perioperative opioids activate toll-like receptor 4 in a manner conducive to inhibiting cancer cell activation [25]. Similarly, opioids may interact with the opioid growth factor (zeta) receptors to inhibit tumour proliferation, and thus the heterogeneity of impact of opioids may be related to the expression profile of various receptors (mu, zeta, TLR) by different cancers.

Opioids have also been shown to interact with inflammatory cytokines such as IL-1, IL-4, IL-6 and tumour necrosis factor which controls gene expression at the μ-opioid receptor [23]. In serum of patients with gastric cancer, morphine has a negative effect on the ratios of CD4+/CD8+ T cells, potentially inducing an immunosuppressive state [26]. Desmond and colleagues demonstrated increased infiltration into breast cancer tissue of NK cells and T helper cells in those receiving paravertebral and propofol anaesthesia (PPA) for breast cancer surgery as opposed to a balanced general anaesthetic technique with opioid analgesia (GA) [27]. Infiltration of these cells into tumour tissue might aid in patient prognostication and outcome [27]. In patients undergoing radical resection of rectal cancer, both oxycodone and morphine were shown to have inhibitory effects on circulating numbers of both T lymphocyte cells and NK cells [28]. Secondary analysis was undertaken of NK cell activity in serum from women ($n = 10$) in an ongoing randomised controlled trial (NCT00418457) undergoing surgery for breast cancer using either propofol and paravertebral technique or GA plus opioid technique [29]. Those who had propofol paravertebral technique versus sevoflurane-opioid technique had greater NK cell cytotoxicity in vitro than their counterparts [29]. Further analysis of this cohort researched neutrophil-lymphocyte ratio (NLR), a marker which may indicate a higher risk of recurrence and poor prognosis [30]. Women who received regional anaesthesia combined with general anaesthesia had lower NLR, demonstrating attenuation of immune response versus combined opioids and volatile anaesthetic [30].

In a study comparing the effects of intravenous morphine, tramadol and ketorolac on stress and immune response in patients undergoing modified radical mastectomy, morphine had the largest effect on reducing circulating T lymphocyte subsets and NK cells, inducing immunosuppression [31]. Ketorolac had the least immunosuppressive effect. The use of fentanyl combined with a non-steroidal anti-inflammatory drug (NSAID) demonstrated decreased levels of VEGF-C, TNF-α and IL-1β in women who had surgery for removal of breast carcinoma [32]. These molecules, which are both inflammatory cytokines (TNF-α and IL-1β) and pro-tumourigenic factors (VEGF-c), are suggested to be involved in tumour proliferation, infiltration and metastasis [32].

Conversely, a study comparing intravenous fentanyl patient-controlled analgesia versus continuous wound infiltration with ropivacaine and intravenous tramadol found no difference in NK cell cytotoxicity and interleukin-2 levels [33] in patients undergoing laparoscopic resection of colorectal cancer. However, a live animal model showed reduced NK cell function following administration of fentanyl versus clonidine and ketamine [34]. Rats undergoing laparotomy with volatile anaesthesia received the three agents (fentanyl, clonidine and ketamine) perioperatively. Analysis of samples was carried out at different time points, pre- and post-operatively assessing NK activity. Fentanyl depressed NK cell activity regardless of whether surgery was performed or not [34].

Of the three classic opioid receptors, μ-opioid receptor has been demonstrated to be over-expressed in certain cancer types [35]. It is thought that agonists at the μ-opioid receptor can lead to stimulation of neoplastic cells and the associated cellular pathways involved in the growth and spread of tumour cells [36]. The μ-opioid receptor has also been implicated in growth factor signalling and proliferation as well as migration and epithelial-mesenchymal transition [37].

Direct effects of opioids can include stimulation of the μ-opioid receptor causing upregulation of angiogenesis. Morphine has been shown to transactivate VEGF via its effects on the μ-opioid receptor [35]. In an early experiment both in vitro on human dermal microvascular endothelial cells and in vivo on nude mice using a breast tumour model, morphine was demonstrated to enhance tumour neovascularisation, as well as stimulating endothelial proliferation, survival and cell cycle progression [12].

Excised breast cancer tissue from patients ($n = 20$) as part of the ongoing trial NCT00418457 was also examined for μ-opioid receptor expression and immune cell infiltration in both pre- and post-operative samples. Patients were randomised to either paravertebral and propofol technique or sevoflurane and opioid technique. While the expression of immune cells (CD56, CD57, CD4 and CD 68) was similar between both groups, μ-opioid receptor expression intensity and number of μ-opioid receptor positive cells were higher in the sevoflurane and opioid group in comparison to the patient's pre-operative biopsy samples [38].

Methylnaltrexone, a μ-opioid receptor antagonist, has been reported to have improved survival in patients with advanced malignancies, particularly in non-small cell lung cancer patients [39]. μ-Opioid receptor polymorphism appears to confer an increased cancer-related survival in breast cancer patients [40]. A post hoc analysis of women with breast cancer and polymorphisms in the A118G variant had reduced 10-year mortality, suggesting a protective effect with the genetic variant in terms of outcomes [40]. These studies, and others [41–44], suggest an importance of the μ-opioid receptor in both the prognosis and overall treatment of some cancers.

The activation of opioid receptors in some cancers, however, may be protective. The activation of opioid receptors by D,L-methadone and subsequent down-regulation of cyclic AMP (cAMP) has been shown to inhibit glioblastoma growth and induce apoptosis as well as improving the effectiveness of chemotherapeutic agents [45]. Similar effects on reduction of cAMP by activation of morphine receptors using D,L-methadone can cause apoptosis and sensitise leukaemia cells to chemotherapeutic agents [46].

The NET-1 gene has also been implicated in promotion of cancer cell migration in a number of different cancer types [47]. In an in vitro study of the effects of morphine on oestrogen receptor-positive and -negative (MCF7) cells, NET-1 expression was found to be increased following its administration, also demonstrating an increase in cell migration by up to 53% [48]. Silencing of the NET-1 gene reversed this effect [48].

Morphine however has been found to have modulatory effects on enzymes that regulate the extracellular matrix [49]. In a murine model of breast tumour metastasis, morphine administration was associated with a reduction in matrix metalloproteinase-9 (MMP-9) enzyme, which is involved in cell invasion and metastasis and an increase in its endogenous inhibitor, TIMP-1 [49].

A number of studies have found no effect of morphine on either increased growth of in situ tumours or increased risk of metastasis. A live mouse model study investigated the effects of morphine on cancer progression, tumour dissemination and effect on minimal residual disease [50]. Analgesic doses of morphine in mice with invasive lobular and HER2+ve breast cancer did not affect the growth of mammary tumours nor the density of micro vessels within the tumour itself [50]. No difference existed in tumour metastasis or outgrowth of residual disease in either the presence or absence of surgical stimuli either [50]. The authors suggested that in analgesic doses, morphine appears to be safe to use in the perioperative period.

In mouse models of Lewis lung carcinoma, morphine in fact decreased tumour growth progression in comparison with saline placebo. Analysis of tumour sections showed decreased angiogenesis and leucocyte infiltration in samples treated with morphine. This was thought to be due mediated by classical opioid receptors as the effect was not seen in mice with MOR knockout genes [51].

Retrospective studies investigating the association between opioid use during primary cancer surgery and cancer recurrence have had equivocal results. Trials vary across the subsets of patients, types of cancer and opioids administered, making results difficult to interpret. Intraoperative consumption of fentanyl in those having resection for colorectal cancer did not show an association with worsened overall survival or recurrence-free survival [52]. Retrospective analysis of patients with oesophageal cancer ($n = 141$) undergoing Ivor Lewis resection found no association with improved overall or recurrence-free survival with respect to opioid use perioperatively [53].

A Danish retrospective study with over 34,000 patients with early-stage breast cancer found no association between opioids and breast cancer recurrence regardless of opioid strength, chronicity of use or cumulative dose [54]. However, this study did not investigate the effects of perioperative or in-hospital use of opioids, investigating only post-diagnosis opioid prescriptions and recurrence [54].

Similarly, large retrospective analysis of non-small cell lung cancer (NSCLC) found no effect on recurrence-free survival with high opioid consumption; however, there was an association between higher opioid consumption and worsened overall survival for stage I patients [55]. In patients with NSCLC, higher post-operative doses of opioids following video-assisted thoracopic surgery were associated with a higher 5-year cancer recurrence rate [56]. Two small trials looking at survival following oral cancer and laryngeal surgery found an association between increased risk of recurrence and mortality with higher intraoperative opioid requirements; however, this was not statistically significant [55, 57].

In summary, the balance of experimental and available retrospective clinical studies suggests conflicting effects of opioids on models of cancer recurrence. The discrepancies in the data may reflect the limitations of both cell culture and animal models. Faithful representation of de novo tumour development and metastasis in humans is difficult to replicate in mice models [58].

To date however, the evidence is not of sufficient strength to demand a change in practice. Indeed, a recent consensus guideline [5] indicates that there is insufficient evidence currently to warrant any change in practice. Opioids should continue to be part of the analgesic regimen for cancer patients if clinically indicated. Prospective randomised control trials are required to identify plausible links between perioperative opioid administration and outcomes for cancer patients.

Local Anaesthetics

Local anaesthetics have well-described anti-inflammatory effects [59]. Lidocaine is an amide local anaesthetic that acts by blocking voltage-gated sodium channels (VGSC) and interrupting synaptic transmission [60]. It also reduces levels of inflammatory markers IL-1, TNF-α and IL-8, reducing the risk of venous thrombosis by inhibiting production of thromboxane B2 [60]. Intravenous lidocaine can reduce post-operative pain following surgery for colon cancer as well as improve recovery in terms of length of stay, opioid requirements and gastrointestinal motility [61, 62].

Local anaesthetic agents appear to have direct effects on cancer cells, blocking a particular type of voltage-gated sodium channels on tumour cells [60]. In vivo evidence points to

lidocaine's ability to reduce migration and viability of breast cancer cells in a study on three types of breast cancer cell lines (MCF-7 luminal A, MDA-MB-231 triple-negative and SKBr3 HER2 positive) versus normal breast epithelium [63•]. The same study reported in vivo data that intraperitoneal lidocaine increased the survival of mice with peritoneal carcinomatosis versus controls [63•].

Bupivacaine, another amide local anaesthetic agent, induced cell death at clinically relevant levels in the breast cancer cell line MCF-7, similar to lidocaine, showing more cytotoxicity for malignant versus non-malignant cells [64]. In other breast cancer cell lines, ropivacaine and lidocaine both have demethylating effects on cancer cells—the same effect was not seen with racemic bupivacaine [65].

Bupivacaine has been found to have direct effects on the inhibition of gastric cancer cell migration in vivo [66]. Both bupivacaine and lidocaine have been found to have modulatory effects in vivo on gene expression of hepatocellular carcinoma cells—inducing apoptosis and a cytostatic effect [67]. Lidocaine and ropivacaine have been found to reduce viability and induce apoptosis in NSCLC cells as well as causing suppression of invasion and migration [68, 69], potentially by inhibition of Src kinase [70]. Src is involved in cell-to-cell adhesion and fibroblast division, promoting cancer cell invasion and metastasis [21].

Intravenous lidocaine has recently been shown to reduce lung metastasis when combined with sevoflurane anaesthesia in a murine model of breast cancer. This effect was not borne out when ketamine/xylazine anaesthesia was used suggesting that lidocaine could have differential interactions with anaesthetic agents, which may influence tumour metastasis [71].

Regional Anaesthesia

The surgical stress response causes a biphasic reaction of increased sympathetic nervous system stimulation and activation of the immune system. Regional anaesthesia is protective against the neuroendocrine element of the stress response, but less so of the cytokine element generated by the body perioperatively [72]. It has been shown to reduce serum levels of cortisol, C-reactive protein and plasma glucose [73]. Regional anaesthesia has also been shown to alter a number of cytokines (IL-1β and IL-10) and matrix metalloproteinases which are involved in perioperative cancer immunity and metastasis in breast cancer patients [74]. The addition of epidural anaesthesia has been shown to reduce plasma concentrations of adrenaline and cortisol in those who were undergoing major abdominal surgery [75]. General anaesthesia combined with epidural anaesthesia also had reduced effect on the concentration of T lymphocyte cells and NK cells in a group of patients undergoing radical resection for gastric cancer [76].

Regional anaesthesia reduces the requirement for alternative forms of analgesia. Opioids, as discussed above, may have an immunosuppressive effect. The use of regional anaesthesia can reduce their use both intra- and post-operatively. Paravertebral blockade [77] and pectoralis plane blocks (I and II) [78] as well as serratus anterior plane blocks [79] can all provide alternative analgesic methods to intravenous opioids. In major breast surgery for cancer, patients receiving single-shot paravertebral blockade had significantly reduced consumption of opioids [80]. Addition of transversus abdominus plane block also reduced pain scores and opioid consumption in patients undergoing laparoscopic high anterior resection [81]. It is unknown whether regional techniques which minimise perioperative opioid requirement during cancer surgery can influence recurrence or metastasis.

Clinical outcomes have been difficult to define in the cancer population. A number of retrospective clinical studies evaluating the effect of a regional anaesthesia technique on an oncological outcome such as recurrence-free survival are summarised in Table 1.

A prospective study ($n = 180$), of patients receiving general anaesthesia versus general anaesthesia with paravertebral block for modified radical mastectomy, found no difference in local recurrence, metastasis or mortality after surgery up to 5 years [96]. However, this study was clearly underpowered to detect long-term outcomes [96]. A small study ($n = 54$) looking at single-injection paravertebral block versus block and local anaesthetic wound infusion found no benefit in extending the length of administration of local anaesthetic in terms of cancer recurrence in patients post mastectomy [97]. This study did not compare their subjects to controls who had not received regional anaesthesia and followed patients up for a minimum of 2 years [97].

Macleod et al. [98] using a retrospective database found no difference in time to biochemical recurrence of prostate cancer between general anaesthesia and opioid analgesia versus general anaesthesia and multimodal analgesia including blocks. Scavonetto et al. [99] suggested an earlier beneficial effect of regional anaesthetic techniques following prostatectomy.

In lung cancer, a recent retrospective analysis comparing analgesic methods of PCA, thoracic epidural and paravertebral block demonstrated a beneficial effect of PVB on overall survival of patients [100•].

Epidural analgesia was associated with improved survival for in patients undergoing pancreatic resection for adenocarcinoma [101]. Retrospective analysis of a cohort of patients in Germany [87] found significantly reduced lengths of intensive care stay and opioid consumption in the epidural anaesthesia group following oesophageal cancer surgery; however, there was no difference between the two groups with regard to mortality or survival. Epidural analgesia for resection of colorectal liver metastasis showed an association between its use

Table 1 Summary of findings of recent retrospective studies on effect of regional anaesthesia and cancer outcomes

Regional technique	Tumour type	Patients (*n*)	Endpoint measured	Publication	Main findings
Epidural	Gastric cancer	4218	Overall survival	Wang et al. [82] *Oncotarget*	Statistically significant improved survival for epidural group—35.1 versus 40.2 months $p < 0.0001$
Epidural	NSCLC	445	Overall survival at 2 and 5 years	Cata et al. [83] *Journal of Clinical Anesthesia*	Type of post-operative analgesia did not affect recurrence-free or disease-free survival
Cervical epidural	Larynx and hypopharynx	65 paired subjects	5-year cancer-free survival Overall survival	Merquiol et al. [84] *Regional Anaesthesia and Pain Medicine*	Combined epidural and general anaesthesia was associated with significantly increased 5-year cancer-free survival ($p = 0.03$) and overall survival ($p = 0.04$)
Epidural	Nephrectomy—partial or radical	438	Overall survival Cancer-specific survival	Kovac et al. [85] *Canadian Journal of Anesthesia/Journal Canadien d'Anesthesie*	Epidural at time of surgery did not
Epidural	Gastric cancer	273	Overall survival	Wang et al. [86] *Medical Science Monitor: International Medical Journal of Experimental And Clinical Research*	Epidural anaesthesia was associated with increased long-term survival in patients up to 64 years old
Epidural	Oesophageal	153 (118 EA)	Cancer recurrence 1-year mortality 5-year survival	Heinrich et al. [87] *Langenbeck's Archives of Surgery*	No significant differences in cancer recurrence, 1-year mortality or 5-year survival
Epidural	Oesophageal	178 propensity matches	Overall survival Time to treatment failure	Li et al. [88] *PLoS One*	No differences in 3-year time to treatment failure or overall survival between epidural and intravenous anaesthesia
Epidural	Colorectal	999 (165 = EA)	Overall survival Time to tumour progression	Tai et al. [89] *PLoS One*	No significant differences in overall survival or progression-free survival in those with epidural analgesia
Epidural	Hepatic metastases from colorectal	179	Cancer-specific survival Overall survival	Doiron et al. [90] *Canadian Urological Association Journal*	No significant differences in overall or cancer-specific survival in those who received epidural analgesia
GA with spinal analgesia (single-shot opioid)	Bladder	195	Overall survival Cancer-specific survival Cancer recurrence	Weingarten et al. [91] *Canadian Journal of Anesthesia*	No differences in relation to all outcomes in those who received spinal analgesia
Spinal	Bladder	231	Time to treatment failure Disease-free survival	Koumpan et al. [92] *The Journal of Urology*	Those receiving spinal anaesthesia had a lower incidence of recurrence ($p = 0.017$) and longer time to disease recurrence ($p = 0.008$)
Neuraxial—spinal and epidural	Prostate	$N = 6261$ general $N = 7504$ neuraxial	Overall survival Biochemical recurrence	Lee et al. [93] *Pain Management*	There was no difference in time to biochemical recurrence with use of neuraxial anaesthesia/analgesia, there appears to be improved overall survival in those who received neuraxial anaesthesia/analgesia
Paravertebral	Breast	86	Disease-free survival Distant recurrence--free overall survival	Kairaluoma et al. [94] *Anticancer Research*	Patients were followed up for 12 years, there was no significant difference between the two groups
Paravertebral	Breast	792 (198 PVB)	Recurrence-free survival Overall survival	Cata et al. [95] *Regional Anesthesia and Pain Medicine*	No significant difference in recurrence-free or overall survival with use of paravertebral block

and improved recurrence-free survival versus intravenous analgesia [102].

A meta-analysis produced in 2014 [103] of ten studies with a combined number of over 3000 patients found no strong signal that there was a difference in the effects on survival and cancer recurrence in general anaesthesia versus combined general-epidural anaesthesia. The authors state the difficulty in generalising the results due to the

heterogenous nature of the data available for analysis at the time [103].

Non-steroidal Anti-inflammatory Agents

Non-steroidal anti-inflammatory (NSAIDs) agents act through the inhibition of COX (cyclooxygenase) enzymes. This stops the subsequent conversion of arachidonic acid into prostaglandin H_2 and its conversion into prostaglandins PGE_2, PGD_2 and PGF_2 as well as prostacyclin and thromboxane A_2 [104]. These prostaglandins are involved in promotion of inflammation, pain and fever. Population-based studies have suggested links between long-term use of NSAIDs, particularly aspirin, and reduced incidence of cancer; in particular, colorectal [105] and breast cancer [106]. Intraoperatively, NSAIDs block tumour-associated inflammation in animal models of cancer, reducing angiogenesis and therefore metastasis [9]. Etodolac, a semi-selective COX-2 inhibitor, counteracted surgical suppression of NK cytotoxicity in mice models of B16F10.9 melanoma and Lewis lung carcinoma [107]. Flurbiprofen axetil is an NSAID that has shown beneficial effects on inflammatory markers in comparison to fentanyl alone in vivo, in breast cancer surgery patients [32]. Levels of VEGF-C, TNF alpha and interleukin-1B were reduced in serum of women receiving a combination of fentanyl and flurbiprofen axetil in comparison to patients receiving fentanyl alone [32].

A retrospective review ($n = 327$) of breast cancer patients undergoing mastectomy with axillary node dissection reported an association between ketorolac, an NSAID, and lower cancer recurrence rate in patients ($p = 0.019$) [108]. When controlled for confounding factors such as age, histological grade and lymph node involvement, the risk of recurrence remained significantly lower in the group receiving intraoperative ketorolac ($p = 0.048$) [108].

A larger single-centre retrospective analysis ($n = 720$) in 2014 on breast cancer patients signalled a link between NSAID use intraoperatively (diclofenac and ketorolac) and improved disease-free and overall survival in breast cancer patients [109]. Data suggests that even with small tumours and conservative surgery, NSAIDs may positively affect breast cancer outcome [109].

A retrospective study examining the link between recurrence-free and overall survival in patients ($n = 1637$) undergoing surgery for NSCLC found no difference in perioperative use of NSAIDs between groups [110]. A study of 1139 patients undergoing surgery for NSCLC found an association between NSAID use and marginal improvement in overall survival of patients with NSCLC but not with recurrence-free survival [111]. In a cohort of 255 patients with lung cancer, retrospective analysis showed a reduction in distant metastasis ($p = 0.009$) in patients who received intraoperative NSAIDs versus those who did not [112].

A more recent retrospective review interrogated records for NSAID use and outcome according to the patient's body mass index (BMI) for breast cancer surgery. Ketorolac was found to be associated with a potentially beneficial effect in reducing distant metastasis in the high BMI group ($p = 0.04$) (BMI > 25) while the effect in the low BMI group (< 25) was not as evident. Diclofenac, also investigated, showed no association with decreased incidence of distant recurrences [113].

While the majority of literature available on NSAIDs are retrospective in nature, an association exists between their administration and reduction in cancer recurrence and metastasis. As with other agents in the perioperative period, prospective randomised control trials are required to investigate potential benefits of these agents perioperatively on cancer recurrence and metastasis.

Anaesthetic Agents

Inhalational Agents

Inhalational anaesthetic agents including sevoflurane and isoflurane are halogenated hydrocarbons and have pro-inflammatory effects [114]. While volatile anaesthetics may provide some benefit by inducing myocardial protection during cardiac surgery [115], this may not be beneficial for the cancer patient. A number of studies looking at volatile anaesthetic agents have implicated an upregulation of HIF-1α, thus conferring a cytoprotective effect on cancer cells at a time of high vulnerability perioperatively [17]. In a prostate cancer cell line (PC3), isoflurane upregulated HIF-1α and its downstream effectors in a dose-dependent manner [16]. The addition of propofol was found to be protective in this instance when used in combination with isoflurane, decreasing the HIF-1α activation [16].

Isoflurane has also been found to enhance renal cancer growth via the same pathway leading to increased expression of VEGF [116]. Isoflurane-exposed RCC4 cancer cells demonstrated an enhanced ability to migrate and rearrange cytoskeleton in their surroundings [116]. In an ovarian cancer model (SKOV3), isoflurane exposure increased levels of insulin-like growth factor, increased expression of VEGF and improved cell migration, increasing the malignant potential of the cells [117].

A systematic review of 20 animal studies found that volatile anaesthetic agents appear to increase both the number and incidence of metastases in experimental cancer models [118]. The authors recommended clinical trials investigating these cited translational difficulties in comparisons between animal and human data, also stating that more research into potential harmful effects of volatile agents should be a priority [118].

There appears to be no perceptible difference between the halogenated agents themselves in terms of recurrence or metastasis of cancer. A study looking at isoflurane, sevoflurane and desflurane found that metastatic-related gene expression profiles were markedly increased following exposure to clinical concentrations of all three volatile agents [119]. In patients having resection for glioblastoma, no survival difference was observed between the groups receiving desflurane or isoflurane intraoperatively.

Xenon, a noble gas, has been clinically investigated in a number of areas but is yet to be employed in routine clinical practice due to cost. Breast adenocarcinoma cells that were exposed to Xenon demonstrated reduced migration and secretion of pro-angiogenic cytokines [120] in comparison to cells exposed to sevoflurane. Nitrous oxide has been found to have no bearing on colorectal cancer recurrence when used in conjunction with isoflurane [121].

Intravenous Agents

The commonest intravenous anaesthetic agent is propofol, which has both anti-inflammatory and anti-oxidative effects [114]. During craniotomy, patients who received propofol anaesthetic demonstrated higher levels of the anti-inflammatory cytokine IL-10 and lower levels of the IL-6/IL-10 ratio [122] suggesting key anti-inflammatory effects of the drug. Propofol also reduces prostaglandin production in a mouse model of inflammation [123]. In a NSCLC cell culture line, propofol was found to have direct effects on reducing the migration and invasion of cancer cells by disrupting the functions of HIF-1α [124]. In a prospective study examining NK cell cytotoxicity in patients undergoing breast cancer resection, propofol anaesthesia with ketorolac demonstrated a preservation of NKCC in comparison to sevoflurane anaesthesia and fentanyl analgesia post operatively [125].

Ketamine has been shown to have the largest effect on retention of lung tumour cells and metastasis versus thiopental and halothane in an inoculation model of breast cancer [126]. It has also been shown in vitro to upregulate anti-apoptosis proteins which may promote breast cancer cell invasion and proliferation [127].

Intravenous Agents Compared to Inhalational Agents

A number of retrospective analyses have been conducted, comparing volatile anaesthesia with intravenous anaesthetic techniques. A large ($n = 706$) retrospective study has demonstrated a statistically significant survival advantage, regardless of tumour-node-metastasis staging in patients who received propofol anaesthesia versus desflurane-based anaesthesia [128].

A small in vivo study comparing expression of pro-oncogenic protein markers in patients who were having resection of head and neck cancer found significant differences in the volatile anaesthesia patients versus the total intravenous anaesthesia (TIVA) with propofol group [129]. Sevoflurane was found to cause a significant increase in the expression of HIF-1α. A recent study comparing sevoflurane anaesthesia and propofol anaesthesia examined the effects of both agents on the expression of a cluster of differentiation enzymes 39 and 73 on regulatory T cells in patients having breast cancer surgery ($n = 201$). The investigators found no significant differences in expression of the enzymes, suggesting minimal effects on perioperative immune activity by both agents [130].

A retrospective analysis of patients undergoing modified radical mastectomy compared propofol-based total intravenous anaesthesia with sevoflurane-based anaesthesia. While the opioid use was higher in the propofol group, there was an association with a lower rate of cancer recurrence at 5 years with propofol [131]. A larger retrospective study investigating outcomes for patients with NSCLC found no difference in overall or recurrence-free survival in patients having TIVA or volatile-based anaesthetic for their initial cancer surgery [53].

A large retrospective single-centre propensity-matched study recently compared patients undergoing general anaesthesia for all cancer surgery using volatile anaesthesia versus total intravenous anaesthesia with propofol and remifentanil. Regardless of patients age, sex, ASA grading, receipt of blood transfusion or metastasis at time of surgery, the volatile anaesthesia group demonstrated an association with a reduction in long-term survival versus the TIVA group [132••].

Undoubtedly, more prospective, clinical, multi-centre research is required to determine the importance of propofol as a preferred anaesthetic agent of choice in cancer anaesthesia. However, it already has a growing body of research to support the theory that it is preferable to volatile agents and a number of trials are ongoing in this area (NCT 03447691, NCT 03034096, NCT 0313710).

Others

Beta-blockade

Perioperatively, catecholamine secretions can increase secondary to the surgical stress response. They are also released in response to tissue damage [133], an inevitable complication of surgery for cancer resection. In ovarian cancer, patients taking non-selective beta-blockers for medical co-morbidities demonstrated a longer overall survival in comparison to their counterparts [134]. Animal laboratory studies suggest both clinical and immunological benefits in combined beta-blockade and COX-2 inhibitors perioperatively [135]. In vivo, a recent phase-II biomarker clinical trial examining combination of propranolol and etodolac in breast cancer patients improved a number of pre-metastatic biomarkers in both the patients' blood samples and the resected tumours [136]. A

larger study looking at patients who underwent modified radical mastectomy found that propranolol can affect the regulatory T cell responses and diminish the response to surgical stress [137]. However, a recently published meta-analysis on intraoperative use of beta-blockers found that their use did not contribute to disease-free survival or overall survival [138••]. Further, large-scale prospective studies are required to investigate the use of beta-blockers in perioperative management of cancer patients.

Oxygen Concentration

Hypoxia is an important factor in the development of solid tumours and improves cancer cell survival and ability to metastasise [139]. While higher concentrations of oxygen are beneficial for the process of wound healing, it is thought that exposure to excess oxygen could promote proliferation of tumour cells [139]. Reactive oxygen species can cause damage to DNA and other crucial cellular components [140]. A 2015 Cochrane review found that there was insufficient evidence to recommend a higher inspired concentration of oxygen during any form of surgery due to the risk of adverse events, including mortality [141].

In a recent laboratory study, exposed breast cancer cell lines MDA-MB 231 and MCF-7 (ER+ and ER−) to 21%, 30%, 60% and 80% concentrations of oxygen showed that exposure to high concentration of oxygen can stimulate migration and secretion of angiogenesis factors in breast cancer cells in vitro [142•]. Furthermore, in a retrospective clinical study among patients randomised to receive different concentrations of oxygen, the incidence of new tumours did not differ between study groups. However, a higher inspired oxygen fraction was associated with shorter cancer-free survival in a post hoc analysis of the PROXI trial cohort. This large randomised control trial followed over 1000 patients who were randomised to either 80% or 30% oxygen while undergoing emergency laparotomy [143].

Alpha-2 Agonists

Dexmedetomidine is an α2-adrenoreceptor agonist that is increasingly used in intensive care and perioperative management. It has a higher affinity for α2 receptors than its long-established counterpart, clonidine [144]. Recent work has cast some controversy on its use in oncological surgery. A 2018 laboratory study noted increased tumour-cell retention and growth of metastases in rat models for lung, breast and colon cancer, suggesting mediation through α2-adrenergic receptors [145]. However, a mechanism of action for this result is yet to be elucidated [144]. Decreased survival was noted in patients who underwent surgery for lung cancer with intraoperative use of dexmedetomidine [146].

Clonidine, which is an important α2-adrenoreceptor agonist used in many surgeries as a method of sparing opioids, has been shown to have no association with shorter recurrence-free or overall survival in a sub-analysis of patients undergoing surgery for breast and lung cancer [147].

Blood Transfusions

Evidence is growing that administration of perioperative allogenic blood transfusions may be associated with poorer outcomes for patients undergoing oncological surgery [148]. A large retrospective analysis of patients with colon cancer found that at 10-year follow-up, patients who received blood transfusions had significantly lower survival rates than non-transfused patients [149]. There was also a higher mortality, local recurrence rate and metastasis rate among the sporadic colon cancer group who received transfusion compared to the hereditary group [149]. Similar results were found in a separate study looking at colorectal carcinoma by the same group [150]. Administration of perioperative blood transfusion was associated with poorer outcomes for those who underwent resection of pancreatic adenocarcinoma [101]. Interestingly, a retrospective study investigating outcomes in radical prostatectomy patients found no correlation between blood transfusion perioperatively and cancer recurrence [151]. A meta-analysis published in 2017 found that perioperative blood transfusions are associated with a detrimental impact on patients with colorectal liver metastasis undergoing hepatectomy [152]. However, these findings could indicate that requirement for transfusion is a hallmark of sicker patients at higher risk of cancer recurrence, rather than a causative factor per se. Well-designed clinical trials are needed in this area to study the effects of allogenic transfusion in this population [148].

Dexamethasone

Perioperative administration of dexamethasone may have immune-modulating effects on cancer cell lines, increasing tumour cell proliferation [153]. Intraoperative use of dexamethasone was associated with improved survival in patients undergoing resection for pancreatic adenocarcinoma [101]. There was no difference in overall or disease-free survival in patients undergoing colectomy who were given pre-operative dexamethasone versus placebo; however, there was an increased rate of distant recurrence in the dexamethasone group [154]. However, in a study of patients undergoing surgery for rectal cancer, those who had perioperative low-dose dexamethasone had poorer 3-year survival outcomes in comparison to those who had not [155]. In NSCLC, dexamethasone was associated with an increased overall survival post-surgery [156], a finding disputed by a later study showing no significant change in recurrence-free or overall survival [157].

Conclusion

While there is a signal suggesting that local anaesthetics might inhibit cancer cell development and opioids might exacerbate metastasis, there is currently an absence of prospective randomised clinical control trials, which is the optimum study design to prove a cause and effect between perioperative intervention and oncologic outcomes (RCT). Studies are primarily retrospective in nature and difficulty lies in separating out the intervention and effect.

Retrospective clinical studies suggest an association between the use of volatile anaesthesia and cancer recurrence, the protective effects of local anaesthetics, regional anaesthesia and propofol, but these are inherently limited in the extent to which they can be interpreted. Therefore, prospective randomised control trials are required to further elucidate any cause and effect that may exist between anaesthetic technique and cancer recurrence and metastasis.

The StEP-COMPAC group has recently recommended use of standardised endpoints in investigation of the perioperative management of cancer patients which would improve benchmarking and allow the pooling of trials for meta-analysis [158••]. Adoption of these endpoints in designing RCTs will allow standardisation of outcomes in terms of the design of RCTs and evaluation of a causal effect of anaesthetic and analgesic technique on patient outcomes, potentially providing a tangible link between the two.

Compliance with Ethical Standards

Conflict of Interest Aislinn Sherwin and Donal J. Buggy declare they have no conflict of interest.

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.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer (Oxford, England : 1990). 2018.
2. Global Burden of Disease Cancer C. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncology. 2017;3(4):524–48.
3. University of Texas MACC. Treatment options - surgery Texas: University of Texas; 2018 [Available from: https://www.mdanderson.org/treatment-options/surgery.html.
4. 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(4):660–4.
5. Buggy DJ, Borgeat A, Cata J, Doherty DG, Doornebal CW, Forget P, et al. Consensus statement from the BJA Workshop on Cancer and Anaesthesia. Br J Anaesth. 2015;114(1):2–3.
6. Behrenbruch C, Shembrey C, Paquet-Fifield S, Molck C, Cho HJ, Michael M, et al. Surgical stress response and promotion of metastasis in colorectal cancer: a complex and heterogeneous process. Clin Exp Metastasis. 2018;35(4):333–45.
7. Lynch ML, Brand MI. Preoperative evaluation and oncologic principles of colon cancer surgery. Clin Colon Rectal Surg. 2005;18(3):163.
8.• Lambert AW, Pattabiraman DR, Weinberg RA. Emerging biological principles of metastasis. Cell. 2017;168(4):670–91 **Review detailing the cellular and molecular mechanisms of metastasis. A useful article explaining the biology of the process.**
9. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. Nat Rev Clin Oncol. 2018;15(4):205–18.
10. Wu WK, Sung JJ, Lee CW, Yu J, Cho CH. Cyclooxygenase-2 in tumorigenesis of gastrointestinal cancers: an update on the molecular mechanisms. Cancer Lett. 2010;295(1):7–16.
11. Perez-Sayans M, Somoza-Martin JM, Barros-Angueira F, Diz PG, Gandara Rey JM, Garcia-Garcia A. Beta-adrenergic receptors in cancer: therapeutic implications. Oncol Res. 2010;19(1):45–54.
12. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law PY, Yee D, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res. 2002;62(15):4491–8.
13. Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploiting the critical perioperative period to improve long-term cancer outcomes. Nat Rev Clin Oncol. 2015;12(4):213–26.
14. Liao D, Johnson RS. Hypoxia: a key regulator of angiogenesis in cancer. Cancer Metastasis Rev. 2007;26(2):281–90.
15. Masoud GN, Li W. HIF-1alpha pathway: role, regulation and intervention for cancer therapy. Acta Pharm Sin B. 2015;5(5):378–89.
16. Huang H, Benzonana LL, Zhao H, Watts HR, Perry NJ, Bevan C, et al. Prostate cancer cell malignancy via modulation of HIF-1alpha pathway with isoflurane and propofol alone and in combination. Br J Cancer. 2014;111(7):1338–49.
17. Tavare AN, Perry NJ, Benzonana LL, Takata M, Ma D. Cancer recurrence after surgery: direct and indirect effects of anesthetic agents. Int J Cancer. 2012;130(6):1237–50.
18. Heaney A, Buggy DJ. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis? Br J Anaesth. 2012;109(Suppl 1):i17–28.
19. Koda K, Saito N, Takiguchi N, Oda K, Nunomura M, Nakajima N. Preoperative natural killer cell activity: correlation with distant metastases in curatively research colorectal carcinomas. Int Surg. 1997;82(2):190–3.
20. Cata JP, Bauer M, Sokari T, Ramirez MF, Mason D, Plautz G, et al. Effects of surgery, general anesthesia, and perioperative epidural analgesia on the immune function of patients with non-small cell lung cancer. J Clin Anesth. 2013;25(4):255–62.
21. Byrne K, Levins KJ, Buggy DJ. Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis? Can J Anaesth. 2016;63(2):184–92.
22. Boland JW, Pockley AG. Influence of opioids on immune function in patients with cancer pain: from bench to bedside. Br J Pharmacol 2017.

23. Connolly C, Buggy DJ. Opioids and tumour metastasis: does the choice of the anesthetic-analgesic technique influence outcome after cancer surgery? Curr Opin Anaesthesiol. 2016;29(4):468–74.
24. Franchi S, Moretti S, Castelli M, Lattuada D, Scavullo C, Panerai AE, et al. Mu opioid receptor activation modulates toll like receptor 4 in murine macrophages. Brain Behav Immun. 2012;26(3): 480–8.
25. Xie N, Matigian N, Vithanage T, Gregory K, Nassar ZD, Cabot PJ, et al. Effect of perioperative opioids on cancer-relevant circulating parameters: mu opioid receptor and toll-like receptor 4 activation potential, and proteolytic profile. Clin Cancer Res. 2018;24(10): 2319–27.
26. Hou M, Zhou NB, Li H, Wang BS, Wang XQ, Wang XW, et al. Morphine and ketamine inhibit immune function of gastric cancer patients by increasing percentage of CD4(+)CD25(+)Foxp3(+) regulatory T cells in vitro. J Surg Res. 2016;203(2):306–12.
27. Desmond F, McCormack J, Mulligan N, Stokes M, Buggy DJ. Effect of anaesthetic technique on immune cell infiltration in breast cancer: a follow-up pilot analysis of a prospective, randomised, investigator-masked study. Anticancer Res. 2015;35(3):1311–9.
28. Cui JH, Jiang WW, Liao YJ, Wang QH, Xu M, Li Y. Effects of oxycodone on immune function in patients undergoing radical resection of rectal cancer under general anesthesia. Medicine. 2017;96(31):e7519.
29. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study. Br J Anaesth. 2014;113(Suppl 1):i56–62.
30. Ni Eochagain A, Burns D, Riedel B, Sessler DI, Buggy DJ. The effect of anaesthetic technique during primary breast cancer surgery on neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and return to intended oncological therapy. Anaesthesia. 2018;73(5):603–11.
31. Bakr MA, Amr SA, Mohamed SA, Hamed HB, Abd El-Rahman AM, Mostafa MA, et al. Comparison between the effects of intravenous morphine, tramadol, and ketorolac on stress and immune responses in patients undergoing modified radical mastectomy. Clin J Pain. 2016;32(10):889–97.
32. Wen Y, Wang M, Yang J, Wang Y, Sun H, Zhao J, et al. A comparison of fentanyl and flurbiprofen axetil on serum VEGF-C, TNF-alpha, and IL-1ss concentrations in women undergoing surgery for breast cancer. Pain Pract. 2015;15(6):530–7.
33. Kim SY, Kim NK, Baik SH, Min BS, Hur H, Lee J, et al. Effects of postoperative pain management on immune function after laparoscopic resection of colorectal cancer: a randomized study. Medicine. 2016;95(19):e3602.
34. Forget P, Collet V, Lavand'homme P, De Kock M. Does analgesia and condition influence immunity after surgery? Effects of fentanyl, ketamine and clonidine on natural killer activity at different ages. Eur J Anaesthesiol. 2010;27(3):233–40.
35. Wigmore T, Farquhar-Smith P. Opioids and cancer: friend or foe? Curr Opin Support Palliat Care. 2016;10(2):109–18.
36. Maher DP, White PF. Proposed mechanisms for association between opioid usage and cancer recurrence after surgery. J Clin Anesth. 2016;28:36–40.
37. Lennon FE, Mirzapoiazova T, Mambetsariev B, Poroyko VA, Salgia R, Moss J, et al. The mu opioid receptor promotes opioid and growth factor-induced proliferation, migration and epithelial mesenchymal transition (EMT) in human lung cancer. PLoS One. 2014;9(3):e91577.
38. KJ Levins, S Prendeville, S Conlon, DJ Buggy The effect of anesthetic technique on μ-opioid receptor expression and immune cell infiltration in breast cancer. J Anesth. 2018.
39. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer. Ann Oncol. 2016;27(11):2032–8.
40. Bortsov AV, Millikan RC, Belfer I, Boortz-Marx RL, Arora H, McLean SA. Mu-opioid receptor gene A118G polymorphism predicts survival in patients with breast cancer. Anesthesiology. 2012;116(4):896–902.
41. Singleton PA, Lingen MW, Fekete MJ, Garcia JG, Moss J. Methylnaltrexone inhibits opiate and VEGF-induced angiogenesis: role of receptor transactivation. Microvasc Res. 2006;72(1–2): 3–11.
42. Mathew B, Lennon FE, Siegler J, Mirzapoiazova T, Mambetsariev N, Sammani S, et al. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. Anesth Analg. 2011;112(3):558–67.
43. Singleton PA, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased mu-opioid receptor expression in metastatic lung cancer. Br J Anaesth. 2014;113(Suppl 1):i103–8.
44. Connolly C, Madden SF, Buggy DJ, Gallagher HC. Expression of anaesthetic and analgesic drug target genes in excised breast tumour tissue: association with clinical disease recurrence or metastasis. PLoS One. 2017;12(5):e0177105.
45. Friesen C, Hormann I, Roscher M, Fichtner I, Alt A, Hilger R, et al. Opioid receptor activation triggering downregulation of cAMP improves effectiveness of anti-cancer drugs in treatment of glioblastoma. Cell cycle. 2014;13(10):1560–70.
46. Friesen C, Roscher M, Hormann I, Fichtner I, Alt A, Hilger RA, et al. Cell death sensitization of leukemia cells by opioid receptor activation. Oncotarget. 2013;4(5):677–90.
47. Lahiff C, Cotter E, Casey R, Doran P, Pidgeon G, Reynolds J, et al. Expression of neuroepithelial transforming gene 1 is enhanced in oesophageal cancer and mediates an invasive tumour cell phenotype. J Exp Clin Cancer Res. 2013;32(1):55.
48. Ecimovic P, Murray D, Doran P, McDonald J, Lambert DG, Buggy DJ. Direct effect of morphine on breast cancer cell function in vitro: role of the NET1 gene. Br J Anaesth. 2011;107(6):916–23.
49. Afsharimani B, Baran J, Watanabe S, Lindner D, Cabot PJ, Parat MO. Morphine and breast tumor metastasis: the role of matrix-degrading enzymes. Clin Exp Metastasis. 2014;31(2):149–58.
50. Doornebal CW, Vrijland K, Hau CS, Coffelt SB, Ciampricotti M, Jonkers J, et al. Morphine does not facilitate breast cancer progression in two preclinical mouse models for human invasive lobular and HER2(+) breast cancer. Pain. 2015;156(8):1424–32.
51. Koodie L, Yuan H, Pumper JA, Yu H, Charboneau R, Ramkrishnan S, et al. Morphine inhibits migration of tumor-infiltrating leukocytes and suppresses angiogenesis associated with tumor growth in mice. Am J Pathol. 2014;184(4):1073–84.
52. Tai YH, Wu HL, Chang WK, Tsou MY, Chen HH, Chang KY. Intraoperative fentanyl consumption does not impact cancer recurrence or overall survival after curative colorectal cancer resection. Sci Rep. 2017;7(1):10816.
53. Oh TK, Kim K, Jheon S, Lee J, Do SH, Hwang JW, et al. Long-term oncologic outcomes for patients undergoing volatile versus intravenous anesthesia for non-small cell lung cancer surgery: a retrospective propensity matching analysis. Cancer Control. 2018;25(1):1073274818775360.
54. Cronin-Fenton DP, Heide-Jorgensen U, Ahern TP, Lash TL, Christiansen PM, Ejlertsen B, et al. Opioids and breast cancer recurrence: a Danish population-based cohort study. Cancer. 2015;121(19):3507–14.
55. Cata JP, Keerty V, Keerty D, Feng L, Norman PH, Gottumukkala V, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. Cancer Med. 2014;3(4):900–8.
56. Maher DP, Wong W, White PF, McKenna R Jr, Rosner H, Shamloo B, et al. Association of increased postoperative opioid

administration with non-small-cell lung cancer recurrence: a retrospective analysis. Br J Anaesth. 2014;113(Suppl 1):i88–94.
57. Patino MA, Ramirez RE, Perez CA, Feng L, Kataria P, Myers J, et al. The impact of intraoperative opioid use on survival after oral cancer surgery. Oral Oncol. 2017;74:1–7.
58. Afsharimani B, Doornebal CW, Cabot PJ, Hollmann MW, Parat M. Comparison and analysis of the animal models used to study the effect of morphine on tumour growth and metastasis. Br J Pharmacol. 2015;172(2):251–9.
59. Chamaraux-Tran TN, Piegeler T. The amide local anesthetic lidocaine in cancer surgery-potential antimetastatic effects and preservation of immune cell function? A narrative review. Front Med. 2017;4:235.
60. Soto G, Naranjo Gonzalez M, Calero F. Intravenous lidocaine infusion. Rev Esp Anestesiol Reanim 2018.
61. Weibel S, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. Br J Anaesth. 2016;116(6):770–83.
62. Tikuisis R, Miliauskas P, Samalavicius NE, Zurauskas A, Samalavicius R, Zabulis V. Intravenous lidocaine for postoperative pain relief after hand-assisted laparoscopic colon surgery: a randomized, placebo-controlled clinical trial. Tech Coloproctol. 2014;18(4):373–80.
63.• Chamaraux-Tran TN, Mathelin C, Aprahamian M, Joshi GP, Tomasetto C, Diemunsch P, et al. Antitumor effects of lidocaine on human breast cancer cells: an in vitro and in vivo experimental trial. Anticancer Res. 2018;38(1):95–105 **In vivo and in vitro murine experiment demonstrating a protective effect of lidocaine against breast cancer cells**.
64. Chang YC, Liu CL, Chen MJ, Hsu YW, Chen SN, Lin CH, et al. Local anesthetics induce apoptosis in human breast tumor cells. Anesth Analg. 2014;118(1):116–24.
65. Lirk P, Hollmann MW, Fleischer M, Weber NC, Fiegl H. Lidocaine and ropivacaine, but not bupivacaine, demethylate deoxyribonucleic acid in breast cancer cells in vitro. Br J Anaesth. 2014;113(Suppl 1):i32–8.
66. Dan J, Gong X, Li D, Zhu G, Wang L, Li F. Inhibition of gastric cancer by local anesthetic bupivacaine through multiple mechanisms independent of sodium channel blockade. Biomed Pharmacother. 2018;103:823–8.
67. Le Gac G, Angenard G, Clement B, Laviolle B, Coulouarn C, Beloeil H. Local anesthetics inhibit the growth of human hepatocellular carcinoma cells. Anesth Analg. 2017;125(5):1600–9.
68. Wang HW, Wang LY, Jiang L, Tian SM, Zhong TD, Fang XM. Amide-linked local anesthetics induce apoptosis in human non-small cell lung cancer. J Thorac Dis. 2016;8(10):2748–57.
69. Piegeler T, Schlapfer M, Dull RO, Schwartz DE, Borgeat A, Minshall RD, et al. Clinically relevant concentrations of lidocaine and ropivacaine inhibit TNFalpha-induced invasion of lung adenocarcinoma cells in vitro by blocking the activation of Akt and focal adhesion kinase. Br J Anaesth. 2015;115(5):784–91.
70. Piegeler T, Votta-Velis EG, Liu G, Place AT, Schwartz DE, Beck-Schimmer B, et al. 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(3):548–59.
71. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, et al. Effect of perioperative lidocaine on metastasis after sevoflurane or ketamine-xylazine anaesthesia for breast tumour resection in a murine model. Br J Anaesth. 2018;121(1):76–85.
72. Hahnenkamp K, Herroeder S, Hollmann MW. Regional anaesthesia, local anaesthetics and the surgical stress response. Best Pract Res Clin Anaesthesiol. 2004;18(3):509–27.
73. O'Riain SC, Buggy DJ, Kerin MJ, Watson RW, Moriarty DC. Inhibition of the stress response to breast cancer surgery by regional anesthesia and analgesia does not affect vascular endothelial growth factor and prostaglandin E2. Anesth Analg. 2005;100(1):244–9.
74. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, et al. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. Reg Anesth Pain Med. 2010;35(6):490–5.
75. Ahlers O, Nachtigall I, Lenze J, Goldmann A, Schulte E, Hohne C, et al. Intraoperative thoracic epidural anaesthesia attenuates stress-induced immunosuppression in patients undergoing major abdominal surgery. Br J Anaesth. 2008;101(6):781–7.
76. Mo H. The impact of different anesthesia methods on stress reaction and immune function of the patients with gastric cancer during peri-operative period. J Med Assoc Thail. 2015;98(6):568–73.
77. Terkawi AS, Tsang S, Sessler DI, Terkawi RS, Nunemaker MS, Durieux ME, et al. Improving analgesic efficacy and safety of thoracic paravertebral block for breast surgery: a mixed-effects meta-analysis. Pain Physician. 2015;18(5):E757–80.
78. Bashandy GM, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med. 2015;40(1):68–74.
79. Hards M, Harada A, Neville I, Harwell S, Babar M, Ravalia A, et al. The effect of serratus plane block performed under direct vision on postoperative pain in breast surgery. J Clin Anesth. 2016;34:427–31.
80. Gacio MF, Lousame AM, Pereira S, Castro C, Santos J. Paravertebral block for management of acute postoperative pain and intercostobrachial neuralgia in major breast surgery. Braz J Anesthesiol. 2016;66(5):475–84.
81. Ris F, Findlay JM, Hompes R, Rashid A, Warwick J, Cunningham C, et al. Addition of transversus abdominis plane block to patient controlled analgesia for laparoscopic high anterior resection improves analgesia, reduces opioid requirement and expedites recovery of bowel function. Ann R Coll Surg Engl. 2014;96(8):579–85.
82. Wang Y, Wang L, Chen H, Xu Y, Zheng X, Wang G. The effects of intra- and post-operative anaesthesia and analgesia choice on outcome after gastric cancer resection: a retrospective study. Oncotarget. 2017;8(37):62658–65.
83. Cata JP, Gottumukkala V, Thakar D, Keerty D, Gebhardt R, Liu DD. Effects of postoperative epidural analgesia on recurrence-free and overall survival in patients with nonsmall cell lung cancer. J Clin Anesth. 2014;26(1):3–17.
84. Merquiol F, Montelimard A-S, 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(5):398–402.
85. Kovac E, Firoozbakhsh F, Zargar H, Fergany A, Elsharkawy H. Perioperative epidural analgesia is not associated with increased survival from renal cell cancer, but overall survival may be improved: a retrospective chart review L'analgésie péridurale périopératoire n'est pas associée à une augmentation de la survie après un cancer des cellules rénales, mais la survie globale pourrait être améliorée: une analyse de dossiers rétrospective. Can J Anesth. 2017;64(7):754–62.
86. Wang J, Guo W, Wu Q, Zhang R, Fang J. Impact of combination epidural and general anesthesia on the long-term survival of gastric cancer patients: a retrospective study. Med Sci Monit. 2016;22:2379–85.
87. Heinrich S, Janitz K, Merkel S, Klein P, Schmidt J. Short- and long term effects of epidural analgesia on morbidity and mortality of esophageal cancer surgery. Langenbeck's Arch Surg. 2015;400(1):19–26.

88. Li W, Li Y, Huang Q, Ye S, Rong T. Short and long-term outcomes of epidural or intravenous analgesia after esophagectomy: a propensity-matched cohort study. PLoS One. 2016;11(4): e0154380.
89. Tai YH, Chang WK, Wu HL, Chan MY, Chen HH, Chang KY. The effect of epidural analgesia on cancer progression in patients with stage IV colorectal cancer after primary tumor resection: a retrospective cohort study. PloS One. 2018;13(7).
90. Christopher Doiron R, Jaeger M, Booth CM, Wei X, Robert SD. Is there a measurable association of epidural use at cystectomy and postoperative outcomes? A population-based study. Canadian Urological Association Journal. 2016;10(9–10):321–7.
91. Weingarten TN, Taccolini AM, Ahle ST, Dietz KR, Dowd SS, Frank I, et al. Perioperative management and oncological outcomes following radical cystectomy for bladder cancer: a matched retrospective cohort study. Can J Anaesth. 2016;63(5):584–95.
92. Koumpan Y, Jaeger M, Mizubuti GB, Tanzola R, Jain K, Hosier G, et al. Spinal anesthesia is associated with lower recurrence rates after resection of nonmuscle invasive bladder cancer. J Urol. 2018;199(4):940–6.
93. Lee BM, Singh Ghotra V, Karam JA, Hernandez M, Pratt G, Cata JP. Regional anesthesia/analgesia and the risk of cancer recurrence and mortality after prostatectomy: a meta-analysis. Pain Manag. 2015;5(5):387–95.
94. Kairaluoma P, Mattson J, Heikkila P, Pere P, Leidenius M. Perioperative paravertebral regional anaesthesia and breast cancer recurrence. Anticancer Res. 2016;36(1):415–8.
95. Cata JP, Chavez-MacGregor M, Valero V, Black W, Black DM, Goravanchi F, et al. The impact of paravertebral block analgesia on breast cancer survival after surgery. Reg Anesth Pain Med. 2016;41(6):696–703.
96. Karmakar MK, Samy W, Lee A, Li JW, Chan WC, Chen PP, et al. Survival analysis of patients with breast cancer undergoing a modified radical mastectomy with or without a thoracic paravertebral block: a 5-year follow-up of a randomized controlled trial. Anticancer Res. 2017;37(10):5813–20.
97. Finn DM, Ilfeld BM, Unkart JT, Madison SJ, Suresh PJ, Sandhu NPS, et al. Post-mastectomy cancer recurrence with and without a continuous paravertebral block in the immediate postoperative period: a prospective multi-year follow-up pilot study of a randomized, triple-masked, placebo-controlled investigation. J Anesth. 2017;31(3):374–9.
98. Macleod LC, Turner RM, 2nd, Lopa S, Hugar LA, Davies BJ, Ben-David B, et al. Effect of multimodal analgesia with paravertebral blocks on biochemical recurrence in men undergoing open radical prostatectomy. Urol Oncol. 2018.
99. Scavonetto F, Yeoh TY, Umbreit EC, Weingarten TN, Gettman MT, Frank I, et al. Association between neuraxial analgesia, cancer progression, and mortality after radical prostatectomy: a large, retrospective matched cohort study. Br J Anaesth. 2014;113(Suppl 1):i95–102.
100.• Lee EK, Ahn HJ, Zo JI, Kim K, Jung DM, Park JH. Paravertebral block does not reduce cancer recurrence, but is related to higher overall survival in lung cancer surgery: a retrospective cohort study. Anesth Analg. 2017;125(4):1322–8 **Retrospective analysis of patients undergoing open thoracotomy for lung cancer—paravertebral analgesia appeared to have a beneficial association with overall survival.**
101. Call TR, Pace NL, Thorup DB, Maxfield D, Chortkoff B, Christensen J, et al. Factors associated with improved survival after resection of pancreatic adenocarcinoma: a multivariable model. Anesthesiology. 2015;122(2):317–24.
102. Zimmitti G, Soliz J, Aloia TA, Gottumukkala V, Cata JP, Tzeng CW, et al. Positive impact of epidural analgesia on oncologic outcomes in patients undergoing resection of colorectal liver metastases. Ann Surg Oncol. 2016;23(3):1003–11.
103. Pei L, Tan G, Wang L, Guo W, Xiao B, Gao X, et al. Comparison of combined general-epidural anesthesia with general anesthesia effects on survival and cancer recurrence: a meta-analysis of retrospective and prospective studies. PLoS One. 2014;9(12): e114667.
104. Gurpinar E, Grizzle WE, Piazza GA. NSAIDs inhibit tumorigenesis, but how? Clin Cancer Res. 2014;20(5):1104–13.
105. Nan H, Hutter CM, Lin Y, Jacobs EJ, Ulrich CM, White E, et al. Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants. JAMA. 2015;313(11):1133–42.
106. Zhong S, Chen L, Zhang X, Yu D, Tang J, Zhao J. Aspirin use and risk of breast cancer: systematic review and meta-analysis of observational studies. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2015;24(11):1645–55.
107. Glasner A, Avraham R, Rosenne E, Benish M, Zmora O, Shemer S, et al. Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a beta-adrenergic antagonist and a cyclooxygenase-2 inhibitor. J Immunol. 2010;184(5):2449–57.
108. Forget P, Vandenhende J, Berliere M, Machiels JP, Nussbaum B, Legrand C, et al. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. Anesth Analg. 2010;110(6):1630–5.
109. Forget P, Bentin C, Machiels JP, Berliere M, Coulie PG, De Kock M. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. Br J Anaesth. 2014;113(Suppl 1):i82–7.
110. Lee BM, Rodriguez A, Mena G, Gottumukkala V, Mehran RJ, Rice DC, et al. Platelet-to-lymphocyte ratio and use of NSAIDs during the perioperative period as prognostic indicators in patients with NSCLC undergoing surgery. Cancer Control. 2016;23(3): 284–94.
111. Choi JE, Villarreal J, Lasala J, Gottumukkala V, Mehran RJ, Rice D, et al. Perioperative neutrophil:lymphocyte ratio and postoperative NSAID use as predictors of survival after lung cancer surgery: a retrospective study. Cancer medicine. 2015;4(6):825–33.
112. Forget P, Machiels JP, Coulie PG, Berliere M, Poncelet AJ, Tombal B, et al. Neutrophil:lymphocyte ratio and intraoperative use of ketorolac or diclofenac are prognostic factors in different cohorts of patients undergoing breast, lung, and kidney cancer surgery. Ann Surg Oncol. 2013;20(Suppl 3):S650–60.
113. Desmedt C, Demicheli R, Fornili M, Bachir I, Duca M, Viglietti G, et al. Potential benefit of intra-operative administration of ketorolac on breast cancer recurrence according to the patient's body mass index. J Natl Cancer Inst 2018.
114. Kim R. Anesthetic technique and cancer recurrence in oncologic surgery: unraveling the puzzle. Cancer Metastasis Rev. 2017;36(1):159–77.
115. Kunst G, Klein AA. Peri-operative anaesthetic myocardial preconditioning and protection - cellular mechanisms and clinical relevance in cardiac anaesthesia. Anaesthesia. 2015;70(4):467–82.
116. Benzonana LL, Perry NJ, Watts HR, Yang B, Perry IA, Coombes C, et al. 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(3):593–605.
117. Luo X, Zhao H, Hennah L, Ning J, Liu J, Tu H, et al. Impact of isoflurane on malignant capability of ovarian cancer in vitro. Br J Anaesth. 2015;114(5):831–9.
118. Hooijmans CR, Geessink FJ, Ritskes-Hoitinga M, Scheffer GJ. A systematic review of the modifying effect of anaesthetic drugs on metastasis in animal models for cancer. PLoS One. 2016;11(5): e0156152.

119. Iwasaki M, Zhao H, Jaffer T, Unwith S, Benzonana L, Lian Q, et al. Volatile anaesthetics enhance the metastasis related cellular signalling including CXCR2 of ovarian cancer cells. Oncotarget. 2016;7(18):26042–56.
120. Ash SA, Valchev GI, Looney M, Ni Mhathuna A, Crowley PD, Gallagher HC, et al. Xenon decreases cell migration and secretion of a pro-angiogenesis factor in breast adenocarcinoma cells: comparison with sevoflurane. Br J Anaesth. 2014;113(Suppl 1):i14–21.
121. Fleischmann E, Marschalek C, Schlemitz K, Dalton JE, Gruenberger T, Herbst F, et al. Nitrous oxide may not increase the risk of cancer recurrence after colorectal surgery: a follow-up of a randomized controlled trial. BMC Anesthesiol. 2009;9:1.
122. Markovic-Bozic J, Karpe B, Potocnik I, Jerin A, Vranic A, Novak-Jankovic V. Effect of propofol and sevoflurane on the inflammatory response of patients undergoing craniotomy. BMC Anesthesiol. 2016;16:18.
123. Inada T, Hirota K, Shingu K. Intravenous anesthetic propofol suppresses prostaglandin E2 and cysteinyl leukotriene production and reduces edema formation in arachidonic acid-induced ear inflammation. J Immunotoxicol. 2015;12(3):261–5.
124. Yang N, Liang Y, Yang P, Ji F. Propofol suppresses LPS-induced nuclear accumulation of HIF-1α and tumor aggressiveness in non-small cell lung cancer. Oncol Rep. 2017;37(5):2611–9.
125. Cho JS, Lee MH, Kim SI, Park S, Park HS, Oh E, et al. The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: a prospective randomized study. Int J Med Sci. 2017;14(10):970–6.
126. 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(5):1331–9.
127. He H, Chen J, Xie WP, Cao S, Hu HY, Yang LQ, et al. Ketamine used as an acesodyne in human breast cancer therapy causes an undesirable side effect, upregulating anti-apoptosis protein Bcl-2 expression. Genet Mol Res. 2013;12(2):1907–15.
128. Wu ZF, Lee MS, Wong CS, Lu CH, Huang YS, Lin KT, et al. Propofol-based total intravenous snesthesia is associated with better survival than desflurane anesthesia in colon cancer surgery. Anesthesiology. 2018.
129. Ferrell JK, Cattano D, Brown RE, Patel CB, Karni RJ. The effects of anesthesia on the morphoproteomic expression of head and neck squamous cell carcinoma: a pilot study. Transl Res. 2015;166(6):674–82.
130. Oh CS, Lee J, Yoon TG, Seo EH, Park HJ, Piao L, et al. Effect of equipotent doses of propofol versus sevoflurane anesthesia on regulatory T cells after breast cancer surgery. Anesthesiology. 2018.
131. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: a retrospective study. Korean journal of anesthesiology. 2016;69(2):126–32.
132.•• Wigmore TJ, Mohammed K, Jhanji S. Long-term survival for patients undergoing volatile versus IV anesthesia for cancer surgery: a retrospective analysis. Anesthesiology. 2016;124(1):69–79 **Large retrospective analysis demonstrating a survival trend in those receviing total intravenous anaesthesia versus volatile anaesthesia.**
133. Neeman E, Zmora O, Ben-Eliyahu S. A new approach to reducing postsurgical cancer recurrence: perioperative targeting of catecholamines and prostaglandins. Clin Cancer Res. 2012;18(18):4895–902.
134. Watkins JL, Thaker PH, Nick AM, Ramondetta LM, Kumar S, Urbauer DL, et al. Clinical impact of selective and nonselective beta-blockers on survival in patients with ovarian cancer. Cancer. 2015;121(19):3444–51.
135. Benish M, Bartal I, Goldfarb Y, Levi B, Avraham R, Raz A, et al. Perioperative use of beta-blockers and COX-2 inhibitors may improve immune competence and reduce the risk of tumor metastasis. Ann Surg Oncol. 2008;15(7):2042–52.
136. Haldar R, Shaashua L, Lavon H, Lyons YA, Zmora O, Sharon E, et al. Perioperative inhibition of beta-adrenergic and COX2 signaling in a clinical trial in breast cancer patients improves tumor Ki-67 expression, serum cytokine levels, and PBMCs transcriptome. Brain Behav Immun. 2018.
137. Zhou L, Li Y, Li X, Chen G, Liang H, Wu Y, et al. Propranolol attenuates surgical stress-induced elevation of the regulatory T cell response in patients undergoing radical mastectomy. J Immunol. 2016;196(8):3460–9.
138.•• Yap A, Lopez-Olivo MA, Dubowitz J, Pratt G, Hiller J, Gottumukkala V, et al. Effect of beta-blockers on cancer recurrence and survival: a meta-analysis of epidemiological and perioperative studies. Br J Anaesth. 2018;121(1):45–57 **Recent meta-analysis of studies examining cancer recurrence, disease-free survival and overall survival with use of beta-blockers.**
139. Moen I, Stuhr LE. Hyperbaric oxygen therapy and cancer–a review. Target Oncol. 2012;7(4):233–42.
140. Lumb AB, Walton LJ. Perioperative oxygen toxicity. Anesthesiol Clin. 2012;30(4):591.
141. Wetterslev J, Meyhoff CS, Jorgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. The Cochrane database of systematic reviews. 2015(6):Cd008884.
142.• Crowley PD, Stuttgen V, O'Carroll E, Ash SA, Buggy DJ, Gallagher HC. Exposure to 60% oxygen promotes migration and upregulates angiogenesis factor secretion in breast cancer cells. Medical gas research. 2017;7(4):226–35 **In vitro analysis of effects of high concentration of oxygen on breast cancer cell's ability to migrate and secrete angiogenesis factors.**
143. Meyhoff CS, Jorgensen LN, Wetterslev J, Siersma VD, Rasmussen LS. Risk of new or recurrent cancer after a high perioperative inspiratory oxygen fraction during abdominal surgery. Br J Anaesth. 2014;113(Suppl 1):i74–81.
144. Freeman J, Buggy DJ. Modelling the effects of perioperative interventions on cancer outcome: lessons from dexmedetomidine. Br J Anaesth. 2018;120(1):15–7.
145. Lavon H, Matzner P, Benbenishty A, Sorski L, Rossene E, Haldar R, et al. Dexmedetomidine promotes metastasis in rodent models of breast, lung, and colon cancers. Br J Anaesth. 2018;120(1):188–96.
146. Cata JP, Singh V, Lee BM, Villarreal J, Mehran JR, Yu J, et al. Intraoperative use of dexmedetomidine is associated with decreased overall survival after lung cancer surgery. J Anaesthesiol Clin Pharmacol. 2017;33(3):317–23.
147. Forget P, Berliere M, Poncelet A, De Kock M. Effect of clonidine on oncological outcomes after breast and lung cancer surgery. Br J Anaesth. 2018;121(1):103–4.
148. Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. Br J Anaesth. 2013;110(5):690–701.
149. Li XX, Meng J, Sun GP, Tang YX, Liang GF, Wang MF, et al. Effects of perioperative blood transfusion on the prognosis in hereditary and sporadic colon cancer. Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals. 2015;20(6–7):481–6.
150. Qiu L, Wang DR, Zhang XY, Gao S, Li XX, Sun GP, et al. Impact of perioperative blood transfusion on immune function and prognosis in colorectal cancer patients. Transfus Apher Sci. 2016;54(2):235–41.

151. Boehm K, Beyer B, Tennstedt P, Schiffmann J, Budaeus L, Haese A, et al. No impact of blood transfusion on oncological outcome after radical prostatectomy in patients with prostate cancer. World J Urol. 2015;33(6):801–6.
152. Lyu X, Qiao W, Li D, Leng Y. Impact of perioperative blood transfusion on clinical outcomes in patients with colorectal liver metastasis after hepatectomy: a meta-analysis. Oncotarget. 2017;8(25):41740–8.
153. Gundisch S, Boeckeler E, Behrends U, Amtmann E, Ehrhardt H, Jeremias I. Glucocorticoids augment survival and proliferation of tumor cells. Anticancer Res. 2012;32(10):4251–61.
154. Singh PP, Lemanu DP, Taylor MH, Hill AG. Association between preoperative glucocorticoids and long-term survival and cancer recurrence after colectomy: follow-up analysis of a previous randomized controlled trial. Br J Anaesth. 2014;113(Suppl 1):i68–73.
155. Yu HC, Luo YX, Peng H, Kang L, Huang MJ, Wang JP. Avoiding perioperative dexamethasone may improve the outcome of patients with rectal cancer. Eur J Surg Oncol. 2015;41(5):667–73.
156. Huang WW, Zhu WZ, Mu DL, Ji XQ, Nie XL, Li XY, et al. Perioperative management may improve long-term survival in patients after lung cancer surgery: a retrospective cohort study. Anesth Analg. 2018;126(5):1666–74.
157. Cata JP, Jones J, Sepesi B, Mehran RJ, Rodriguez-Restrepo A, Lasala J, et al. Lack of association between dexamethasone and long-term survival after non-small cell lung cancer surgery. J Cardiothorac Vasc Anesth. 2016;30(4):930–5.
158.•• Buggy DJ, Freeman J, Johnson MZ, Leslie K, Riedel B, Sessler DI, et al. Systematic review and consensus definitions for standardised endpoints in perioperative medicine: postoperative cancer outcomes. Br J Anaesth. 2018;121(1):38–44 **Consensus guidelines from a number of clinical researchers indicating standardised endpoints to allow pooling and bench-marking of trials in anaesthesia and cancer research.**