Can J Anesth/J Can Anesth (2016) 63:184–192
DOI 10.1007/s12630-015-0523-8

REVIEW ARTICLE/BRIEF REVIEW

Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis?

Les techniques d'anesthésie et d'analgésie lors d'une chirurgie de cancer primitif peuvent-elle affecter la récurrence ou la métastase?

Kathryn Byrne, MD · Kirk J. Levins, PhD · Donal J. Buggy, MD

Received: 16 June 2015 / Revised: 22 September 2015 / Accepted: 15 October 2015 / Published online: 23 October 2015

Abstract

Purpose *Mortality among cancer patients is more commonly due to the effects of metastasis and recurrence as opposed to the primary tumour. Various perioperative factors have been implicated in tumour growth, including anesthetic agents and analgesia techniques. In this narrative review, we integrate this information to present a summary of the best available evidence to guide the conduct of anesthesia for primary cancer surgery.*

Source *We conducted a search of the PubMed database up to May 31, 2015 to identify relevant literature using the search terms "anesthesia and metastases", "anesthetic drugs and cancer", "volatile anesthetic agents and cancer", and "anesthetic technique and cancer".*

Principal findings *There is conflicting evidence regarding volatile agents; however, the majority of studies are in vitro, suggesting that these agents are associated with enhanced expression of tumourigenic markers as well as both proliferation and migration of cancer cells. Nitrous oxide has not been shown to have any effect on cancer recurrence. Local anesthetic agents may reduce the incidence of cancer recurrence through systemic anti-inflammatory action in addition to direct effects on the proliferation and migration of cancer cells. Nonsteroidal anti-inflammatory drugs affect cancer cells via inhibition of cyclooxygenase 2 (COX-2), which leads to reduced resistance of the cancer cell to apoptosis and reduced production of prostaglandins by cancer cells. Nonsteroidal anti-inflammatory drugs also suppress the cancer cell growth cycle through effects independent of COX-2 inhibition. Opioids have been shown to inhibit the function of natural killer cells and to stimulate cancer cell proliferation through effects on angiogenesis and tumour cell signalling pathways. Supplemental oxygen at the time of surgery has a proangiogenic effect on micrometastases, while the use of perioperative dexamethasone does not affect overall rates of cancer survival.*

Conclusions *Current laboratory research suggests that perioperative interventions may impact recurrence or metastasis through effects on cancer cell signalling, the immune response, or modulation of the neuroendocrine stress response. Further evidence is awaited from prospective randomized-controlled trials. Meanwhile, with limited data upon which to make strong recommendations, anesthesiologists should seek optimal anesthesia and analgesia for their patients based on individual risk-benefit analysis and best available evidence on outcomes other than cancer recurrence.*

Résumé

Objectif *Parmi les patients cancéreux, la mortalité est très souvent due aux effets de la métastase et à une récurrence plutôt qu'à la tumeur primitive. Divers facteurs périopératoires pourraient inciter la croissance tumorale, notamment les agents anesthésiques et les techniques d'analgésie. Dans ce compte rendu narratif, nous*

Author contributions *Kathryn Byrne*, *Kirk J. Levins* and *Donal J. Buggy* contributed substantially to the conception and design of the manuscript.

K. Byrne, MD · K. J. Levins, PhD · D. J. Buggy, MD (✉)
Department of Anaesthesia, Mater Misericordiae University Hospital, School of Medicine, University College Dublin, Dublin, Ireland
e-mail: donal.buggy@ucd.ie

réunissons ces informations et résumons les meilleures données probantes actuelles afin de guider la conduite de l'anesthésie pour les chirurgies de cancer primitif.

Source *Nous avons effectué une recherche dans la base de données PubMed jusqu'au 31 mai 2015 afin d'identifier les publications pertinentes à l'aide des termes de recherche suivants: « anesthesia ET metastases », « anesthetic drugs ET cancer », « volatile anesthetic agents ET cancer », et « anesthetic technique ET cancer » (soit 'anesthésie ET métastases', 'médicaments anesthésiques ET cancer', 'agents anesthésiques volatils ET cancer', et 'technique d'anesthésie ET cancer', respectivement).*

Constatations principales *Les données probantes sont conflictuelles en ce concerne les agents volatils; toutefois, il convient de souligner que la majorité des études ont été réalisées in vitro, ce qui laisse à penser que ces agents sont associés à une expression plus forte des marqueurs oncogènes ainsi qu'à la prolifération et à la migration des cellules cancéreuses. Le protoxyde d'azote n'a pas été associé à un quelconque effet sur la récurrence de cancer. Les anesthésiques locaux pourraient réduire l'incidence de récurrence de cancer grâce à leur action anti-inflammatoire systémique, en plus de leurs effets directs sur la prolifération et la migration des cellules cancéreuses. Les anti-inflammatoires non stéroïdiens affectent les cellules cancéreuses en inhibant la cyclo-oxygénase 2 (COX-2), ce qui réduit la résistance des cellules cancéreuses à l'apoptose et diminue la production de prostaglandines par les cellules cancéreuses. Les anti-inflammatoires non stéroïdiens suppriment également le cycle de croissance des cellules cancéreuses grâce à d'autres effets, indépendants de l'inhibition de la COX-2. Il a été démontré que les opioïdes inhibaient la fonction des cellules tueuses naturelles et stimulaient la prolifération des cellules cancéreuses via leurs effets sur l'angiogenèse et les voies de signalisation des cellules tumorales. L'oxygénothérapie pendant la chirurgie a un effet proangiogénique sur les micrométastases, alors que le recours à la dexaméthasone périopératoire n'affecte pas les taux globaux de survie au cancer.*

Conclusion *Selon les recherches actuelles en laboratoire, les interventions périopératoires pourraient avoir un impact sur la récurrence ou la métastase en ayant un effet sur la signalisation des cellules cancéreuses, la réponse immunitaire ou la modulation de la réponse neuroendocrinienne au stress. Des données probantes supplémentaires provenant d'études randomisées contrôlées prospectives sont attendues. D'ici-là, en raison du peu de données disponibles pour émettre des recommandations rigoureuses, nous invitons les anesthésiologistes à choisir la meilleure anesthésie et la meilleure analgésie pour leurs patients selon une analyse individuelle des risques et bienfaits et les meilleures données probantes disponibles concernant les pronostics autres que la récurrence du cancer.*

In many parts of the world, cancer, together with cardiovascular disease, is now the number one cause of death. Furthermore, its incidence is increasing, with 14.1 million new cases of cancer diagnosed worldwide in 2012. Lung, breast, bowel, and prostate cancer are currently the most prevalent types.[1] Importantly, mortality in many cancer patients is commonly the result of recurrence or metastasis rather than an effect of the primary tumour itself.

It is almost a decade since the hypothesis was put forward that perioperative factors, including anesthetic and analgesic management, may influence cancer recurrence or metastasis.[2,3] Earlier still, breast cancer patients who had received halothane anesthesia showed increased survival rates when compared with those who had received ether anesthesia.[4] A further direct effect of anesthetic agents on cancer cell biology was proposed in 1981 when the effect of four commonly used anesthetic drugs was examined on the postoperative growth of mouse tumours. This work showed accelerated growth of lung metastases and the development of secondary tumours in organs not otherwise commonly associated with metastases.[5]

The challenge of conducting large multicentre randomized-controlled trials that address this question cannot be underestimated. The main limitation of the majority of work published to date is its retrospective design. There are frequent uncontrolled and unrecognized biases and differing criteria regarding such data as the stage of cancer at the time of surgery, the underlying tumour biology, the surgical skill of the clinicians, and the effects of perioperative adjuvant therapies such as chemotherapy or radiotherapy.[6,7]

This present narrative review summarizes the current state of evidence for many regularly used drugs and techniques for anesthesia and analgesia in the perioperative period and addresses their actual or potential effects on cancer cell biology and the risk of cancer metastasis.

The literature in this article was retrieved from a search of the PubMed database up to May 31, 2015. Search terms included "anesthesia and metastases", "anesthetic drugs and cancer", "volatile anesthetic agents and cancer", and "anesthetic technique and cancer". Results were restricted to the English language. Relevant articles were also obtained from the articles identified in the literature review, and all primary sources were retrieved. Two authors then reviewed these articles for suitability.

Current laboratory research points to the existence of signals suggesting that perioperative interventions may

impact recurrence or metastasis through effects on cancer cell signalling, the immune response, and modulation of the neuroendocrine stress response. Meanwhile, we await substantiated evidence from prospective randomized-controlled trials (RCTs) (Table). Understanding the molecular components and processes involved in metastatic and local spread may lead to a more targeted approach to prevent cancer recurrence as a consequence of perioperative management.[8] Several animal model studies have shown that tumour growth and metastasis are enhanced by a combination of processes that occur in the perioperative period, including inadvertent dispersal of tumour cells during surgical manipulation, the suppression of cell-mediated immunity by the stress response, and the increased expression of proangiogenic factors by tumour cells that are an essential component of metastatic spread.[7]

The recent "Consensus statement from the BJA Workshop on Cancer and Anaesthesia" acknowledges insufficient evidence to support a change in clinical practice and calls for further research, preferably in the form of RCTs, to investigate the effects of volatile agents, opioids, nonsteroidal anti-inflammatory drugs (NSAIDS), and regional anesthetic techniques on cancer recurrence and metastasis.[9] Indeed, although the evidence is inconclusive, the possibility that anesthesia may contribute to the recurrence of cancer cannot be ignored and requires definitive prospective RCTs to test whether a link of cause and effect exists between the most promising perioperative interventions and the risk of recurrence.

Are volatile anesthetic agents safe to use in cancer patients?

This question arises because an increasing number of studies have investigated the direct effects of volatile anesthetic agents on cancer cell biology, and results have shown that they induced mitogenesis, angiogenesis, and metastasis in tumours. One such study investigated the effects of isoflurane on the expression of tumourigenic markers, including insulin-like growth factor (IGF-1) and proliferative capacity in ovarian cancer cells. The study results showed that isoflurane significantly increased expression of IGF-1 and IGF-1 receptors, cell cycle progression, and cell proliferation in ovarian cancer cells 24 hr after exposure. It also showed increased expression of the angiogenic markers vascular endothelial growth factor (VEGF) and angiopoietin-1 after isoflurane exposure together with an enhanced angiogenesis. Enhanced cell migration of cancer cells after isoflurane exposure was associated with increased production of metalloproteinases 2 and 9, enzymes that play a key role in the degradation of extracellular matrix and thus facilitate local spread of tumour cells. This effect was terminated when IGF-1 signalling was blocked either by a neutralizing antibody or by small interfering ribonucleic acids.[10] On this theme, results of a small RCT among 40 patients presenting for colon cancer surgery showed that serum levels of proangiogenic factors VEGF-C and transforming growth factor beta-1 increased significantly in the patients who received volatile-based anesthesia *vs* propofol-epidural anesthesia.[11]

Table 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	Koo
00938171	Breast cancer	Propofol sedation with local infiltration *vs* general anesthesia with sevoflurane	Chang
418457	Breast cancer	Regional plus TIVA *vs* general anesthesia + opioids	Buggy
2005770	Breast cancer	TIVA *vs* inhalational anesthesia	Beck Schimmer
1916317	Breast cancer	Peritumoral local anesthesia *vs* no peritumoral local anesthesia	Badwe
2314871	Colon cancer	Perioperative analgesia with morphine PCA *vs* epidural	Berta
684229	Colon cancer	Regional *vs* general anesthesia	Kurz
2326727	Colon cancer	Regional *vs* general anesthesia	Reytman
2326727	Colon cancer	Epidural anesthesia *vs* no epidural anesthesia	Reytman
2335151	Pancreatic Cancer	TIVA *vs* inhalational anesthesia	Beck Schimmer
1854021	Tongue Cancer	TIVA *vs* combined intravenous-inhalational anesthesia *vs* inhalational anesthesia	Zhang
1588847	Malignant melanoma	Regional *vs* general anesthesia	Van Aken
01975064	Colon/Rectal/Breast cancer	TIVA *vs* sevoflurane-maintained anesthesia	Bergkvist

NCT = ClinicalTrials.gov clinical trial number; PCA = patient-controlled analgesia; TIVA = total intravenous anesthesia

Stem cells possess the ability to self-perpetuate and give rise to mature cells of a particular tissue through differentiation.[12] Cancer stem cells are relatively rare cells with indefinite proliferative potential that drive the formation and growth of tumours.[13] Studies investigating the effect of volatile agents on a range of cancer stem cells have shown varying results. One such study evaluating the response of glioma stem cell exposure to varying durations and concentrations of sevoflurane compared with controls showed increased proliferation of cancer cells and a capacity for self-renewal after sevoflurane. This was associated with increased expression of hypoxia-inducible factor (HIF) protein.[14] Similarly, HIF was the mechanism underpinning the enhanced migration effect of isoflurane on renal cancer cells *in vitro*.[15]

In a recent study by Jaura *et al.,* breast cancer cells were exposed to serum from females (n = 20) who underwent surgery for biopsy-proven primary breast cancer. The women were enrolled in a multicentre prospective clinical trial (ClinicalTrials.gov number, NCT00418457) and randomized to receive either propofol-paravertebral anesthesia or a volatile agent and opioid-based anesthetic technique for breast cancer excision. Study results showed less cancer cell apoptosis in the group receiving propofol-paravertebral anesthesia.[16]

Kvolik *et al.* investigated the cytotoxic and antiproliferative effects of sevoflurane in clinically relevant concentrations and duration of exposure on different human cancer cell lines, colon adenocarcinoma cells, and laryngeal carcinoma cells, *in vitro*.[17] They found that the apoptotic ratio had increased significantly 24 hr after anesthesia and was associated with increased expression of *p53* and *caspase-3* genes in colon cancer cells. Nevertheless, they also noted a decreased expression in laryngeal cancer cells, suggesting any potentially beneficial effect of this volatile agent to increase cancer cell apoptosis may be dependent on the tumour cell line.

On balance, while there remains conflicting evidence regarding the potential deleterious effects of volatile agents from the available evidence of *in vitro* studies to date, there is insufficient evidence to justify avoidance of these agents in cancer patients.

The immunosuppressive effect of nitrous oxide, mediated through selective inhibition of methionine synthase and therefore DNA, purine, and thymidylate synthesis, causes depressed macrophage and natural killer (NK) cell function.[18,19] The recent ENIGMA-II trial found that use of nitrous oxide did not increase major postoperative complications at 30 days, including myocardial infarction, and there was no evidence of an aggravating effect relating to cancer recurrence or mortality.[20] Prior to the ENIGMA-II trial, a study with a specific focus on nitrous oxide and cancer assessed the recurrence rate of colon cancer in a prospective randomized trial of 204 patients assigned to either 65% nitrous oxide or nitrogen during surgery. This study found a similar rate of recurrence in the two groups, suggesting that nitrous oxide has no impact on cancer recurrence.[21]

On the subject of specific anesthetic gases, the noble gas xenon has been tested clinically and found to have many desirable properties, but its progression into routine clinical practice has been limited in part by its prohibitive cost. Recent *in vitro* studies conducted on its effects on breast cancer cell biology found that acute exposure of breast adenocarcinoma cells to xenon inhibited migration without affecting viability and was associated with decreased secretion of pro-angiogenic cytokines RANTES/CCL5.[22] Notably in this study, effects of xenon were visible within one hour of exposure of cancer cells to xenon. Although the mechanism by which xenon affects cancer biology is yet to be fully elucidated, the authors of this study suggest that the action of xenon at the glycine binding site of the N-methyl-D-aspartate receptor causes a decrease in breast cancer cell migration. Xenon is also thought to bind to the Kir6.2 subunit of the adenosine triphosphate-dependent potassium channel, causing cytoskeletal changes that are involved in tumourigenesis and cell migration.[23]

Local anesthetics and neuraxial anesthesia

Some retrospective clinical studies have found an association between the use of regional anesthesia and reduced cancer metastasis. Regardless of the local anesthetic agent employed, regional anesthetic techniques are associated with decreased activation of the stress response.[24] This allows for a reduction in opioid usage as well as decreased release of endogenous opioids[25] and, consequently, less immunosuppression. It has also been proposed that local anesthetic agents *per se* reduce the incidence of cancer recurrence through anti-inflammatory action as well as direct effects on the proliferation and migration of cancer cells.[26] Both lidocaine and ropivacaine have been shown to have antiproliferative effects on cancer cells *in vitro*.[27] While these drugs are known to act via sodium (Na^+) channel inhibition, their potentially beneficial effect in cancer cells is mediated by the alternative mechanism via inhibition of the proto-oncogene Src. The functions of Src include regulation of cell-to-cell adhesion and involvement in fibroblast cell division, and its overexpression in solid tumours is associated with tumour cell progression, invasion, and metastasis. The inhibition of Src thereby plays a role in preventing the release of downstream mediators of cancer cell migration and metastasis. Lidocaine, in clinically relevant plasma concentrations, has been shown to

suppress proliferation of the cancer cell via a direct inhibitory effect on the epidermal growth factor receptor, which is a tyrosine kinase receptor essential for the proliferation and differentiation of epithelial cells and tumours of epithelial cell origin.[28] Amide local anesthetics have also been shown to be potent inhibitors of voltage-activated Na^+ channels and in this way inhibit metastatic colon cancer cell invasion.[29]

At clinically relevant concentrations, lidocaine also has an action on the methylation in tumour cells. The demethylation of DNA in breast cancer cells is associated with decreased tumour progression through activation of tumour suppressor genes.[30] Lirk *et al.* found that lidocaine and, to a lesser extent, ropivacaine and bupivacaine exert demethylating effects on breast cancer cells *in vitro*.[31] Furthermore, lidocaine, in combination with the chemotherapeutic agent 5-aza-2'-deoxycytidine, exhibits additive demethylating effects.[31]

Therefore, existing evidence from laboratory cell culture models clearly suggests that amide local anesthetics have a direct therapeutic effect of inhibiting cancer cell metastasis. To date, there is a lack of *in vivo* animal model data evaluating this hypothesis. It also seems warranted to conduct a prospective RCT that tests the effects of administering intravenous lidocaine during primary cancer surgery on long-term cancer outcome.

Studies concerning the use of neuraxial or regional anesthesia in cancer surgery have shown conflicting results with respect to the association of reduced cancer recurrence with cancer spread.[32,33] In addition to the demethylating effects of local anesthetics, another principal mechanism by which neuraxial anesthesia might reduce cancer spread is via either an opioid sparing effect or attenuation of the surgical stress response and its immunosuppressive consequences. Compared with general anesthesia alone, the addition of spinal blockade to general anesthesia was shown to attenuate metastasis significantly in rats inoculated with a strain of breast adenocarcinoma. Furthermore, this effect was inversely related to NK cell expression, i.e., metastasis was reduced when NK cell expression increased.[34] A recent large (n = 3,284) retrospective analysis examined the long-term outcomes (e.g., systemic cancer progression, recurrence, prostate cancer mortality, and all-cause mortality) of patients who underwent radical retropubic prostatectomy for adenocarcinoma. Their results showed general anesthesia alone was associated with an increased risk for systemic progression (hazard ratio [HR], 2.81; 95% confidence interval [CI], 1.31 to 6.05; P = 0.008) and higher all-cause mortality (HR, 1.32; 95% CI, 1.00 to 1.74; P = 0.047) compared with the combination of general and neuraxial anesthesia. There was also a trend towards an increased risk of death from prostate cancer in those patients who received only general anesthesia (adjusted HR, 2.2; 95% CI, 0.88 to 5.60; P = 0.091).[35]

Nevertheless, although there are multiple retrospective analyses evaluating regional anesthesia techniques in many kinds of cancer, there are conflicting results.[36] A recent translational study conducted on a subset of patients enrolled in an ongoing multicentre RCT in breast cancer patients found that the serum of women (n = 10) with breast cancer randomized to receive propofol-paravertebral anesthesia for excisional surgery preserved NK immune cell cytotoxicity and breast cancer cell apoptosis to a greater extent than the serum of women randomized to receive standard volatile-based general anesthesia with opioid analgesia.[37] Practitioners may choose to promote regional anesthesia with propofol-based general anesthesia to their cancer patients for many reasons other than the possibility of an effect on cancer recurrence. The continuing prospective RCT (ClinicalTrials.gov number, NCT00418457) may prove to address whether this technique has a cause and effect link to cancer recurrence.

Myles *et al*. conducted a follow-up subgroup analysis of the MASTER study from 2000[38] in an effort to identify whether performing an epidural block at the time of major abdominal surgery for cancer was associated with reduced cancer recurrence and improved survival. Of the 915 patients enrolled in the MASTER trial, 446 patients were included in the subgroup analysis, 216 did not receive an epidural, and 230 received an epidural at the time of their surgery. The results showed that the median time to recurrence of cancer or death was 2.8 yr (95% CI, 0.7 to 8.7) in the control group and 2.6 yr (95% CI, 0.7 to 8.7) in the epidural group (P = 0.61). Recurrence-free survival was similar in both the epidural and the control group (HR, 0.95; 95% CI, 0.76 to 1.17; P = 0.61).[39]

Nonsteroidal anti-inflammatory agents

It is suggested that the effect of NSAIDs on disease progression may be tumour-specific and mediated through a direct effect on cyclooxygenase-2 (COX-2) receptors expressed by cancer cells as well as by indirect antagonism of the production of prostaglandins by NK cells. The expression of COX-2 in many types of cancer cells is associated with an increased resistance to apoptosis and the production of prostaglandins involved in tumour growth.[40] Both chronic and acute use of NSAIDs as analgesics in the cancer patient have been associated with tumour regression, presumably through the inhibition of COX-2 and prostaglandin synthesis, although alternative COX-independent pathways may also play a role in COX-2 selective NSAIDs.[41-43] The effects of celecoxib, a selective COX-2 inhibitor, and SC-560, a selective COX-1 inhibitor, on cell survival, cell cycle

distribution, and apoptosis in colon cancer cell lines were evaluated *in vivo* and *in vitro*. Results showed that both drugs induced a G0/G1 phase block and reduced cell survival. These effects were independent of COX-2 expression by the cancer cell.[41] In another study comparing the effects of celecoxib and rofecoxib on human prostate cancer cell lines—which, notably, did not express COX-2—celecoxib was found to suppress the growth of these cell lines. Treatment of these cell lines with celecoxib led to a marked decrease in the expression of the protein-coding gene, cyclin D1, which is essential for cell cycle progression to synthesis or during cell DNA replication.[42]

Regarding acetylsalicylic acid, a meta-analysis of five large RCTs that randomized patients to either acetylsalicylic acid 75 mg daily *vs* control for the prevention of vascular events found that allocation to acetylsalicylic acid reduced risk of cancer with distant metastasis (all cancers: HR, 0.64; 95% CI, 0.48 to 0.84; $P = 0.001$; adenocarcinoma: HR, 0.54; 95% CI, 0.38 to 0.77; $P < 0.001$; other solid cancers: HR, 0.82; 95% CI, 0.53 to 1.28; $P = 0.39$), mainly due to a reduction in the proportion of adenocarcinomas that had metastatic *vs* local disease (odds ratio, 0.52; 95% CI, 0.35 to 0.75; $P < 0.001$).[43]

In a retrospective analysis of 720 patients conducted by Forget *et al.*, the intraoperative use of ketorolac or diclofenac in breast cancer patients was associated with prolonged disease-free survival and overall survival.[44] In the same group of patients, a raised neutrophil:lymphocyte ratio in the preoperative period was associated with reduced survival. These results differ from a similar retrospective study among 1,111 patients who underwent radical prostatectomy for localized prostate cancer. Findings indicated that the perioperative use of ketorolac failed to show any survival benefit.[45]

Currently available evidence suggests merit in using perioperative NSAIDs to lessen the risk of cancer recurrence; however, individual patient decisions whether or not to use them should be based on an individual risk-benefit assessment of their likely value in a particular case. Proof of any effect on cancer recurrence must await results of prospective RCTs.

Opioids

Opioids remain a cornerstone in the management of both acute postoperative pain and cancer-related pain in palliative care. Nevertheless, there is a strong suggestion from both retrospective clinical trials and experimental studies that opioids may promote cancer progression and reduce long-term survival.

Opioids have been shown to have numerous direct effects on cancer cells, which culminate in facilitating the spread of malignant cells. Proposed mechanisms include the direct promotion of cancer cell growth and inhibition of cellular immunity. Opioids are capable of stimulating angiogenesis partly by activating COX-2. This increases the production of prostaglandin E2, which promotes angiogenesis and directly affects tumour growth.[46] Morphine contributes to the proliferation and survival of cancer cells by activating mitogen-activated protein kinase and Akt signalling pathways in tumour cells.[47]

Several studies have focused on the actions of the μ-opioid receptor (MOR) in the regulation of tumour growth and metastasis.[48,49] The overexpression of MOR has been shown in both lung[50,51] and prostate cancer. [52] The theory regarding MOR involvement in metastasis is further supported by the diminished progression of lung carcinoma in MOR knockout mice treated with the opioid receptor antagonist naltrexone.[53] Morphine does not influence the initiation of tumour development; rather, it affects the progression of established breast tumour, as recently shown in a transgenic mouse study that found significantly decreased survival in a mouse model of breast adenocarcinoma.[54] In the same study, it was found that morphine promoted lymphangiogenesis, mast cell activation and degranulation, and increased levels of inflammatory cytokines, tryptase, and substance P. In addition, the morphine-treated mice had increased tumour burden and decreased duration of survival.[54]

In an immunohistochemical study on the effect of MOR on metastasis, patients who had excision of non-small cell lung carcinoma were evaluated for their MOR status. There was a direct correlation between MOR expression and the extent of metastasis in these patients.[48]

A further study carried out on the aforementioned breast cancer specimens from patients previously enrolled in the ongoing RCT (ClinicalTrials.gov number, NCT00418457) has investigated the effect of anesthetic technique on immune cell expression in breast cancer tissue. It was found that women with breast cancer randomized to receive propofol-paravertebral anesthesia ($n = 12$) for surgical excision had a higher expression of NK cell infiltration than women with standard vapour general anesthesia with opioid analgesia ($n = 16$). This finding suggests that anesthetic technique may have an early effect on immune function in breast cancer tissue.[55]

Supplemental oxygen effects

Excess oxygen administration has been associated with increased morbidity and mortality across a range of medical conditions.[56,57] Several studies in postoperative patients treated regularly with high fractional inspired oxygen concentrations have shown varying results,

particularly in relation to the development of surgical site infections in the postoperative period.[58,59] In a retrospective follow-up of a previous RCT evaluating the effect of different concentrations of oxygen administered during primary cancer surgery, the incidence of new or recurrent cancers was similar after 80% or 30% oxygen [140 of 678 patients (21%) in the 80% group *vs* 150 of 699 patients (21%) in the 30% group]. Nevertheless, cancer-free survival was significantly shorter in the 80% oxygen group (HR, 1.18; 95% CI, 1.01 to 1.42; $P = 0.04$), and the median time between surgery and new cancer diagnosis was also significantly shorter (80% group, 335 days *vs* 30% group, 434 days; $P = 0.047$).[60] As well as promoting the production of erythropoietin and new vessel formation,[61] it is possible that supplemental oxygen at the time of surgery has a proangiogenic effect on micrometastases, which, in the absence of hyperoxia, may have otherwise remained quiescent. Oxygen therapy for prolonged periods is also associated with the formation of reactive oxygen species and DNA damage.[62]

Dexamethasone

Steroids administered in the perioperative period have immune-modulating effects that include suppression of NK cells and enhanced resistance of the tumour cell to apoptosis.[63] Dexamethasone is an antiemetic frequently used in the perioperative period, and it may potentially be pro-analgesic.[64] A recent study reporting the five-year follow-up of patients who received dexamethasone or placebo before elective colectomy for colon cancer as part of a previous RCT[65] found no difference in overall or disease-free survival between the two groups. However, patients who had received a dose of dexamethasone (8 mg) had a significantly higher rate of distant recurrence compared with those who received placebo (six patients in the dexamethasone group *vs* one patient in the placebo group; $P = 0.04$) and a non-significant trend towards higher cancer-specific mortality.[66]

Blood transfusion

Over at least the past decade, the practice of blood transfusion has been influenced by the principle of avoidance until an anemia trigger of < 7 g·dL^{-1} has been reached. Nevertheless, results of a recent randomized trial ($n = 198$) of postoperative cancer patients, where patients were randomized to receive either a liberal transfusion regimen (transfused if hemoglobin [Hb] < 9 g·dL^{-1}) *vs* a restrictive regimen (transfused only if Hb < 7 g·dL^{-1}), showed that the composite (95% CI) of morbidity and mortality at 30 days after surgery for abdominal cancer was 19.6% *vs* 35.6%, respectively (95% CI, 12.9 to 28.6 in the liberal regimen *vs* 95% CI, 27 to 45.4 in the restrictive regimen; $P = 0.012$). This suggests that a more liberal transfusion regimen may be beneficial, at least in terms of early postoperative morbidity.[67] This does not affect the long-term association between transfusion and increased cancer recurrence.[68]

Conclusion

In conclusion, a major limitation of available evidence is the fact that the *in vitro* conditions of most studies do not faithfully replicate cancer cell biology conditions *in vivo*. Therefore, there is a high degree of speculative extrapolation of results to the clinical setting. Although prospective RCTs (Table) are ongoing and we await their results, there is also a growing recognition that choice of anesthetic technique and agent at the time of cancer surgery may have significant long-term implications in tumour growth and spread.

With increasing numbers of patients presenting for cancer surgery and increasing signals suggesting possible long-term effects of anesthetic technique on cancer growth, there is a growing need to fund prospective multicentre RCTs that can address these questions with more certainty. Meanwhile, anesthesiologists and their patients should seek optimal anesthesia and analgesia based on individual risk-benefit analysis and best available evidence on outcomes other than cancer recurrence. Such decisions should be made on the basis of established evidence around optimal analgesia, avoidance of unwanted side effects, or compatibility with a patient's comorbidities, rather than on any putative benefit in cancer patients.

Conflicts of interest None declared.

References

1. *Siegel R*, *Naishadham D*, *Jemal A*. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10-29.
2. *Exadaktylos AK*, *Buggy DJ*, *Moriarty DC*, *Mascha E*, *Sessler DI*. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006; 105: 660-4.
3. *Lin L*, *Liu C*, *Tan H*, *Ouyang H*, *Zhang Y*, *Zeng W*. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. Br J Anaesth 2011; 106: 814-22.
4. *Fried IA*. The influence of the anaesthetic on survival rates of breast cancer patients after surgery. Int J Cancer 1977; 20: 213-8.
5. *Shapiro J*, *Jersky J*, *Katzav S*, *Feldman M*, *Segal S*. Anesthetic drugs accelerate the progression of postoperative metastases of mouse tumors. J Clin Invest 1981; 68: 678-85.
6. *Ash SA*, *Buggy DJ*. Does regional anaesthesia and analgesia or opioid analgesia influence recurrence after primary cancer

surgery? An update of available evidence. Best Pract Res Clin Anaesthesiol 2013; 27: 441-56.
7. *Heaney A*, *Buggy DJ*. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis? Br J Anaesth 2012; 109(Suppl 1): i17-28.
8. *Chiang AC*, *Massague J*. Molecular basis of metastasis. N Engl J Med 2008; 359: 2814-23.
9. *Buggy DJ*, *Borgeat A*, *Cata J*, *et al*. Consensus statement from the BJA Workshop on Cancer and Anaesthesia. Br J Anaesth 2015; 114: 2-3.
10. *Luo X*, *Zhao H*, *Hennah L*, *et al*. Impact of isoflurane on malignant capability of ovarian cancer in vitro. Br J Anaesth 2015; 114: 831-9.
11. *Xu YJ*, *Chen WK*, *Zhu Y*, *Wang SL*, *Miao CH*. Effect of thoracic epidural anaesthesia on serum vascular endothelial growth factor C and cytokines in patients undergoing anaesthesia and surgery for colon cancer. Br J Anaesth 2014; 113(Suppl 1): i49-55.
12. *Reya T*, *Morrison SJ*, *Clarke MF*, *Weissman IL*. Stem cells, cancer, and cancer stem cells. Nature 2001; 414: 105-11.
13. *Clarke MF*, *Fuller M*. Stem cells and cancer: two faces of eve. Cell 2006; 124: 1111-5.
14. *Shi QY*, *Zhang SJ*, *Liu L*, *et al*. Sevoflurane promotes the expansion of glioma stem cells through activation of hypoxia-inducible factors in vitro. Br J Anaesth 2015; 114: 825-30.
15. *Benzonana LL*, *Perry NJS*, *Watts HR*, *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: 593-605.
16. *Jaura AI*, *Flood G*, *Gallagher HC*, *Buggy DJ*. Differential effects of serum from patients administered distinct anaesthetic techniques on apoptosis in breast cancer cells in vitro: a pilot study. Br J Anaesth 2014; 113(Suppl 1): i63-7.
17. *Kvolik S*, *Dobrosevic B*, *Marczi S*, *Prlic L*, *Glavas-Obrovac L*. Different apoptosis ratios and gene expressions in two human cell lines after sevoflurane anaesthesia. Acta Anaesthesiol Scand 2009; 53: 1192-9.
18. *Schneemilch CE*, *Hachenberg T*, *Ansorge S*, *Ittenson A*, *Bank U*. Effects of different anaesthetic agents on immune cell function in vitro. Eur J Anaesthesiol 2005; 22: 616-23.
19. *Sanders RD*, *Weimann J*, *Maze M*. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anesthesiology 2008; 109: 707-22.
20. *Myles PS*, *Leslie K*, *Chan MT*, *et al*. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. Lancet 2014; 384: 1446-54.
21. *Fleischmann E*, *Marschalek C*, *Schlemitz K*, *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.
22. *Ash SA*, *Valchev GI*, *Looney M*, *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.
23. *Ru Q*, *Tian X*, *Wu YX*, *Wu RH*, *Pi MS*, *Li CY*. Voltage-gated and ATP-sensitive K+ channels are associated with cell proliferation and tumorigenesis of human glioma. Oncol Rep 2014; 31: 842-8.
24. *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: 244-9.
25. *Chae BK*, *Lee HW*, *Sun K*, *Choi YH*, *Kim HM*. The effect of combined epidural and light general anesthesia on stress hormones in open heart surgery patients. Surg Today 1998; 28: 727-31.
26. *Piegeler T*, *Votta-Velis EG*, *Liu G*, *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: 548-59.
27. *Martinsson T*. Ropivacaine inhibits serum-induced proliferation of colon adenocarcinoma cells in vitro. J Pharmacol Exp Ther 1999; 288: 660-4.
28. *Sakaguchi M*, *Kuroda Y*, *Hirose M*. The antiproliferative effect of lidocaine on human tongue cancer cells with inhibition of the activity of epidermal growth factor receptor. Anesth Analg 2006; 102: 1103-7.
29. *Baptista-Hon DT*, *Robertson FM*, *Robertson GB*, *et al*. Potent inhibition by ropivacaine of metastatic colon cancer SW620 cell invasion and NaV1.5 channel function. Br J Anaesth 2014; 113(Suppl 1): i39-48.
30. *Navada SC*, *Steinmann J*, *Lubbert M*, *Silverman LR*. Clinical development of demethylating agents in hematology. J Clin Invest 2014; 124: 40-6.
31. *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.
32. *Biki B*, *Mascha E*, *Moriarty DC*, *Fitzpatrick JM*, *Sessler DI*, *Buggy DJ*. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiology 2008; 109: 180-7.
33. *Gottschalk A*, *Ford JG*, *Regelin CC*, *et al*. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. Anesthesiology 2010; 113: 27-34.
34. *Bar-Yosef S*, *Melamed R*, *Page GG*, *Shakhar G*, *Shakhar K*, *Ben-Eliyahu S*. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. Anesthesiology 2001; 94: 1066-73.
35. *Scavonetto F*, *Yeoh TY*, *Umbreit EC*, *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.
36. *Conrick-Martin I*, *Kell MR*, *Buggy DJ*. Meta-analysis of the effect of central neuraxial regional anesthesia compared with general anesthesia on postoperative natural killer T lymphocyte function. J Clin Anesth 2012; 24: 3-7.
37. *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.
38. *Rigg JR*, *Jamrozik K*, *Myles PS*, *et al*. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet 2002; 359: 1276-82.
39. *Myles PS*, *Peyton P*, *Silbert B*, *et al*. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. BMJ 2011; 342: d1491.
40. *Eisinger AL*, *Prescott SM*, *Jones DA*, *Stafforini DM*. The role of cyclooxygenase-2 and prostaglandins in colon cancer. Prostaglandins Other Lipid Mediat 2007; 82: 147-54.
41. *Grosch S*, *Tegeder I*, *Niederberger E*, *Brautigam L*, *Geisslinger G*. COX-2 independent induction of cell cycle arrest and apoptosis in colon cancer cells by the selective COX-2 inhibitor celecoxib. FASEB J 2001; 15: 2742-4.
42. *Patel MI*, *Subbaramaiah K*, *Du B*, *et al*. Celecoxib inhibits prostate cancer growth: evidence of a cyclooxygenase-2-independent mechanism. Clin Cancer Res 2005; 11: 1999-2007.
43. *Rothwell PM*, *Wilson M*, *Price JF*, *Belch JF*, *Meade TW*, *Mehta Z*. Effect of daily aspirin on risk of cancer metastasis: a study of

incident cancers during randomised controlled trials. Lancet 2012; 379: 1591-601.
44. *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.
45. *Forget P*, *Tombal B*, *Scholtes JL*, *et al*. Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? Eur J Anaesthesiol 2011; 28: 830-5.
46. *Amano H*, *Ito Y*, *Suzuki T*, *et al*. Roles of a prostaglandin E-type receptor, EP3, in upregulation of matrix metalloproteinase-9 and vascular endothelial growth factor during enhancement of tumor metastasis. Cancer Sci 2009; 100: 2318-24.
47. *Gupta K*, *Kshirsagar S*, *Chang L*, *et al*. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res 2002; 62: 4491-8.
48. *Singleton PA*, *Mirzapoiazova T*, *Hasina R*, *Salgia R*, *Moss J*. Increased μ-opioid receptor expression in metastatic lung cancer. Br J Anaesth 2014; 113(Suppl 1): i103-8.
49. *Zylla D*, *Kuskowski MA*, *Gupta K*, *Gupta P*. Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer. Br J Anaesth 2014; 113(Suppl 1): i109-16.
50. *Lennon FE*, *Mirzapoiazova T*, *Mambetsariev B*, *Salgia R*, *Moss J*, *Singleton PA*. Overexpression of the μ-opioid receptor in human non-small cell lung cancer promotes Akt and mTOR activation, tumor growth, and metastasis. Anesthesiology 2012; 116: 857-67.
51. *Fujioka N*, *Nguyen J*, *Chen C*, *et al*. Morphine-induced epidermal growth factor pathway activation in non-small cell lung cancer. Anesth Analg 2011; 113: 1353-64.
52. *Zylla D*, *Gourley BL*, *Vang D*, *et al*. Opioid requirement, opioid receptor expression, and clinical outcomes in patients with advanced prostate cancer. Cancer 2013; 119: 4103-10.
53. *Mathew B*, *Lennon FE*, *Siegler J*, *et al*. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. Anesth Analg 2011; 112: 558-67.
54. *Nguyen J*, *Luk K*, *Vang D*, *et al*. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer. Br J Anaesth 2014; 113(Suppl 1): i4-13.
55. *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: 1311-9.
56. *Austin MA*, *Wills KE*, *Blizzard L*, *Walters EH*, *Wood-Baker R*. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. BMJ 2010; 341: c5462.
57. *Cabello JB*, *Burls A*, *Emparanza JI*, *Bayliss S*, *Quinn T*. Oxygen therapy for acute myocardial infarction. Cochrane Database Syst Rev 2013; 8: CD007160.
58. *Staehr AK*, *Meyhoff CS*, *Rasmussen LS*, *PROXI Trial Group*. Inspiratory oxygen fraction and postoperative complications in obese patients: a subgroup analysis of the PROXI trial. Anesthesiology 2011; 114: 1313-9.
59. *Meyhoff CS*, *Wetterslev J*, *Jorgensen LN*, *et al*. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. JAMA 2009; 302: 1543-50.
60. *Meyhoff CS*, *Jorgensen LN*, *Wetterslev J*, *Siersma VD*, *Rasmussen LS*, *PROXI Trial Group*. 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.
61. *Hopf HW*, *Gibson JJ*, *Angeles AP*, *et al*. Hyperoxia and angiogenesis. Wound Repair Regen 2005; 13: 558-64.
62. *Lumb AB*, *Walton LJ*. Perioperative oxygen toxicity. Anesthesiol Clin 2012; 30: 591-605.
63. *Gundisch S*, *Boeckeler E*, *Behrends U*, *Amtmann E*, *Ehrhardt H*, *Jeremias I*. Glucocorticoids augment survival and proliferation of tumor cells. Anticancer Res 2012; 32: 4251-61.
64. *De Oliveira GS*, *Almeida MD*, *Benzon HT*, *McCarthy RJ*. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2011; 115: 575-88.
65. *Zargar-Shoshtari K*, *Sammour T*, *Kahokehr A*, *Connolly AB*, *Hill AG*. Randomized clinical trial of the effect of glucocorticoids on peritoneal inflammation and postoperative recovery after colectomy. Br J Surg 2009; 96: 1253-61.
66. *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.
67. *de Almeida JP*, *Vincent JL*, *Galas FR*, *et al*. Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial. Anesthesiology 2015; 122: 29-38.
68. *Amato A*, *Pescatori M*. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev 2006; 1: CD005033.