Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis?

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Summary. Cancer is a leading cause of morbidity and mortality worldwide and the ratio of incidence is increasing. Mortality usually results from recurrence or metastases. Surgical removal of the primary tumour is the mainstay of treatment, but this is associated with inadvertent dispersal of neoplastic cells into the blood and lymphatic systems. The fate of the dispersed cells depends on the balance of perioperative factors promoting tumour survival and growth (including surgery per se, many anaesthetics per se, acute postoperative pain, and opioid analgesics) together with the perioperative immune status of the patient. Available evidence from experimental cell culture and live animal data on these factors are summarized, together with clinical evidence from retrospective studies. Taken together, current data are sufficient only to generate a hypothesis that an anaesthetic technique during primary cancer surgery could affect recurrence or metastases, but a causal link can only be proved by prospective, randomized, clinical trials. Many are ongoing, but definitive results might not emerge for a further 5 yr or longer. Meanwhile, there is no hard evidence to support altering anaesthetic technique in cancer patients, pending the outcome of the ongoing clinical trials.

Keywords: anaesthesia; metastases; recurrence, cancer; regional, cancer

Introduction

Despite significant advances in oncological therapies, cancer remains a major cause of morbidity and mortality. During 2008, 12.7 million new cancer cases were diagnosed worldwide, with 7.6 million cancer-related deaths during that period. In the USA it is estimated that 1500 people die from cancer every day, whereas in the UK, more than one in three people will develop some form of cancer during their lifetime.1 2 The incidence rate of cancer continues to increase; therefore, anaesthetists are facing the challenge of managing cancer patients with increasing frequency.3 In many cancers, surgical resection to de-bulk and remove the primary tumour is the mainstay of treatment; however, metastatic recurrence is common. Recent commentary suggests that a number of perioperative factors can directly affect cancer cells and also impact on cell-mediated immunity, thereby potentially promoting the development of metastasis (Table 1).4–6

Here we review the literature on the hypothesis that anaesthetic and analgesic techniques for primary cancer surgery influence long-term outcomes, elucidating the biology of cancer cells and the perioperative factors that could influence metastasis, including the available clinical data.

The literature in this review was obtained from searches of PubMed© until August 2012. Results included all languages. Search terms included ‘anaesthesia and cancer recurrence’, ‘mechanism of tumour metastasis’, ‘intravenous anaesthesia and cancer’, ‘volatile inhalational drugs and cancer’, ‘surgery and immune function’, ‘opioids and cancer’, ‘COX inhibitors and cancer’, ‘regional anaesthesia and cancer’, ‘anxiety and cancer’, ‘red cell transfusion and cancer’, and ‘hypothermia and cancer’. Relevant references from the articles identified were also reviewed.

Cancer cell biology and the mechanism of metastasis

Metastasis is a complex process, the onset of which is heralded by the detachment of metastatic cells from the primary tumour and completion signified by tumour proliferation within a distant organ. Establishment of an independent blood supply (angiogenesis) and evasion of the host’s immune defences are essential processes for successful tumour dissemination.7 The outcome of the metastatic
process is dependent upon a myriad of interactions between the immune system of hosts and the tumour’s propensity to metastasize. Tumour cells result from a single cell that has undergone multiple cycles of division and mutation. This mutated cell is ‘genetically unstable’, making it susceptible to the acquisition of additional mutations.

The tumour cell becomes refractory to normal signalling cues that regulate cell division and uncontrolled cellular proliferation ensues. Extensive angiogenesis must occur to fulfil the increasing demands of the evolving tumour. Indeed, tumours cannot survive beyond 2 mm in diameter without angiogenesis. The process of angiogenesis is stimulated by the release of pro-angiogenic factors from the tumour, including vascular endothelial growth factor (VEGF) and prostaglandin E2.

Table 1: How perioperative factors could potentially influence cancer recurrence and metastasis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Stimulates neuroendocrine and cytokine stress response</td>
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<tr>
<td></td>
<td>Suppresses cell-mediated immunity</td>
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<tr>
<td></td>
<td>Disperses tumour ‘emboli’</td>
</tr>
<tr>
<td></td>
<td>Promotes tumour growth and metastasis in animal models</td>
</tr>
<tr>
<td>Pain</td>
<td>Animal studies indicate that inadequately treated postoperative pain suppresses NK cell activity and promotes metastasis</td>
</tr>
<tr>
<td>Volatile anaesthesia</td>
<td>Possibly alters the activity of leucocytes</td>
</tr>
<tr>
<td></td>
<td>Associated with induction of apoptosis in lymphocytes in vitro</td>
</tr>
<tr>
<td>Propofol</td>
<td>Attenuates cancer cell migration, proliferation, and metastasis in vitro</td>
</tr>
<tr>
<td></td>
<td>Possible COX inhibitor</td>
</tr>
<tr>
<td>Opioids</td>
<td>MORs are over-expressed in certain cancers</td>
</tr>
<tr>
<td></td>
<td>Inhibit cell-mediated and humoral immunity</td>
</tr>
<tr>
<td></td>
<td>Promote tumour cell migration, proliferation, and cancer gene expression in human cells in vitro</td>
</tr>
<tr>
<td></td>
<td>Facilitate angiogenesis</td>
</tr>
<tr>
<td>NSAIDs/COX inhibitors</td>
<td>COX over-expressed in many cancers</td>
</tr>
<tr>
<td></td>
<td>PGs inhibit NK cell cytotoxicity and modulate the tumour microenvironment</td>
</tr>
<tr>
<td></td>
<td>Long-term use associated with reduced incidence of cancer</td>
</tr>
<tr>
<td>Allogeneic blood transfusion</td>
<td>Associated with immunosuppression, increased risk of cancer recurrence, and reduced survival</td>
</tr>
<tr>
<td>Psychological stress</td>
<td>Animal and clinical evidence of an association between stress, depression, and cancer progression</td>
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<tr>
<td></td>
<td>Activates HPA-axis and sympathetic nervous system</td>
</tr>
<tr>
<td></td>
<td>Contributes to perioperative immunosuppression</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Stimulates sympathetic nervous system and glucocorticoid release</td>
</tr>
<tr>
<td></td>
<td>Increases bleeding and allogeneic blood transfusion</td>
</tr>
<tr>
<td></td>
<td>Suppresses cell-mediated and humoral immunity</td>
</tr>
</tbody>
</table>

Cancer and the immune system

Cell-mediated immunity forms the primary defence against the invasion of tumour cells and its major components include natural killer (NK) cells, cytotoxic T cells, mononuclear cells, and dendritic cells. NK cells are large, granular cytotoxic lymphocytes that recognize tumour cells spontaneously, without prior sensitization, and induce lysis. There is an association between stress-induced attenuation of NK cell activity and the promotion of breast tumour growth and metastasis in a rat model and patients with low levels of NK cells and increased risk of developing cancer, or metastases after cancer surgery. Despite intact immunity, some tumour cells evade the host’s defences and continue to grow. The inflammatory state induced by the developing tumour is conducive to recruitment of immune cells to its ‘microenvironment’. Recruited immune cells might not exhibit the normal protective response that leads to tumour cell eradication. Release of pro-inflammatory cytokines by these immune cells, and by the tumour itself, can tip the balance in favour of tumour progression.
The immune system is modulated by multiples of cytokines, some of which are associated with promotion of cancer, while others resist it. Manipulation of the immune system to produce an enhanced anti-tumour response could be utilized as an adjuvant oncological therapy. Recombinant NK T cells, for example, have proposed therapeutic potential. A promising survival benefit was observed when rats received ‘immunostimulation’ therapy perioperatively.17

The effect of surgery per se on host immune function and metastasis

Surgical excision is frequently an essential component of cancer management and it offers the best opportunity for a good prognosis in patients with solid tumours.5,6 However, it is known that surgical excision of the tumour can inadvertently facilitate the metastatic process.18 Even with successful excision to histologically negative margins, ‘minimal residual disease’ remains, as a result of inadvertent dispersal of tumour ‘emboli’ during surgery, or pre-existing ‘micrometastases’. The ongoing presence of neoplastic cells in the circulation 24 h after resection is independently associated with increased risk of cancer recurrence.19 The fate of this minimal residual disease is critically dependent upon the perioperative immune competence of the host. However, major surgery is associated with a neuroendocrine and cytokine ‘stress response’,20 which induces transient suppression of cell-mediated immunity during this vulnerable period, when it might be determined whether metastasis will be established or eradicated.21

Several studies using animal models have demonstrated that tumour growth and metastasis are enhanced by surgery. For example, it was demonstrated in a mouse model that laparotomy increased the number of liver metastases from ~15 to 34.22 The proposed mechanisms by which surgery promotes metastasis include the following factors:

1) Inadvertent dispersal of tumour cells during surgical manipulation

Peripheral blood and peritoneal fluid was analysed from patients undergoing surgery for colorectal cancer. Patients who had detectable tumour cells in the blood/peritoneal fluid after operation had a significantly shorter disease-free survival (43.9 months) compared with patients who had no detectable cells (80.5 months). Some patients who had no detectable tumour cells before operation were found to have detectable cells after operation, suggesting that surgery had dislodged neoplastic cells from the primary tumour.23

2) Suppression of cell-mediated immunity

Surgery and the stress response have been shown to suppress cell-mediated immunity, NK cell activity in particular, in experimental and clinical studies. The degree of immunosuppression depends on the degree of surgical trauma and therefore, on the intensity of the stress response. Surgical trauma stimulates the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. The resultant stress response is characterized by the release of catecholamines and prostaglandins. Laparotomy was associated with a significant increase in tumour retention (LTR) in a rat model; however, a combination of β-antagonism and COX inhibition reduced LTR and restored NK cell function.24 Interestingly when this regimen was combined with immunostimulation, a synergistic effect was observed.25

3) Angiogenesis

Many of the stimulants of angiogenesis are increased after operation, including VEGF and transforming growth factor (TGF) β. Increased postoperative plasma levels of VEGF (1385 pg ml⁻¹) compared with preoperative levels (806 pg ml⁻¹) were demonstrated in patients undergoing mastectomy for breast cancer25. Matrix metalloproteinases (MMPs) are proteolytic enzymes that facilitate the metastatic process by penetrating the extracellular matrix and basement membrane of host cells. Deegan and colleagues26, in a randomized clinical study, demonstrated that regional anaesthesia combined with propofol attenuated the effect of surgery on MMPs compared with balanced general anaesthesia (GA) with opioid analgesia. Angiogenesis is regulated by a delicate balance between the opposing forces of pro-angiogenic factors (VEGFs, fibroblast growth factor, and TGF-β) and anti-angiogenic factors (e.g. angiostatin). Surgery augments angiogenesis by promoting:

(a) Increased plasma levels of VEGF—in a mouse model, the stress of surgery (laparotomy or mastectomy) or chronic stress significantly increased tumour mass associated with increased postoperative levels of VEGF.27-28
(b) Decreased plasma levels of endostatin and angiostatin—endostatin is an endogenous anti-angiogenic mediator, formed by the fragmentation of collagen and significantly reduced lung cancer metastasis in a mouse model.29

Effect of anaesthesia per se on host immune function and cancer

Experimental evidence from a rat inoculation model of breast cancer suggests that ketamine, thiopental, and older volatile anaesthetics increase tumour metastasis, in an inverse relationship with NK cell activity.30 Sevoflurane binds lymphocyte antigens, interfering with their activity.31 Isoflurane and sevoflurane have been shown to induce apoptosis in human T-lymphocytes in vitro in a dose-dependent manner.32 While activation of an inositol triphosphate (IP₃) mechanism has been found by which isoflurane induces apoptosis in chicken-derived B-lymphocytes in vitro.33

A recent review suggested that volatile anaesthetics upregulate hypoxia-inducible factor (HIF-1α) in neoplastic cells, which increases angiogenesis and is associated with poor
patient prognosis. An experimental study using human colon cancer cells found that isoflurane exposure (30 min at 1.2%) was not associated with induction of apoptosis in these cells in vitro. Furthermore, a number of volatile agents altered gene expression in two separate cancer cell lines, breast carcinoma, and neuroblastoma in vitro. On the other hand, another in vitro study demonstrated that pre-treating human neutrophils with sevoflurane and desflurane inhibited the release of MMP-9 by ~40% (for both agents). As a result, migration of colon cancer cells was inhibited.

**Nitrous oxide**

Nitrous oxide has been associated with a number of immune modulating effects in experimental and clinical studies. A follow-up study of a previous randomized, controlled trial initially designed to evaluate surgical site infection, in which patients who underwent colectomy for cancer were randomized to receive either 65% nitrous oxide (N₂O) and oxygen or 65% nitrogen and oxygen, in combination with isoflurane and remifentanil. Patients who received N₂O showed no significant difference in cancer recurrence compared with those receiving nitrogen and oxygen (P=0.72).

**Propofol**

Propofol significantly decreased the production of prostaglandin E₂ by human monocytes in vitro. However, it is unclear whether this effect is related to the proposed anti-neoplastic effect of propofol. In a rat model of breast cancer, propofol was not associated with an increase in LTR, nor did it suppress NK cell cytotoxicity.

**Ketamine**

Ketamine has exhibited immunomodulatory effects on macrophages, lymphocytes, and mast cells in experimental studies. It inhibited dendritic cell-mediated maturation of T cells in a mouse model; however, the ketamine concentration used was two to three times higher than that used in the clinical setting. In another study, ketamine (10 mg kg⁻¹) exerted inhibitory effects on NK cell cytotoxicity in vitro, using a rat model. The effect of low-dose ketamine (0.15 mg kg⁻¹) i.v., 5 min before induction of GA, on immune function in patients undergoing elective abdominal surgery in a randomized controlled trial, was examined. It indicated that ketamine attenuated production of the pro-inflammatory cytokines, IL-6, and TNF-α and suppressed NK cell cytotoxicity after operation.

**Local anaesthetics**

Local anaesthetics (LAs) have proposed cytotoxic effects on neoplastic cells. An anti-proliferative effect on human tongue cancer cells, by inhibiting epidermal growth factor, was exhibited by lidocaine in vitro. Lidocaine, bupivacaine, and ropivacaine reduced mesenchymal stem cell proliferation in vitro and transcription pathways related to initiation of neoplasia and metastasis were also inhibited. LAs have also been reported to alter the DNA methylation status of certain cancer cell types and have been associated with the reactivation of tumour suppressor genes.

LAs have also been associated with cytotoxic effects on T-lymphoma cell lines in vitro. Apoptosis was observed at lower concentrations, while necrosis was seen at higher concentrations. Eight LAs were studied in total and each exhibited varying cytotoxic effects, which appeared to correlate with their lipophilicity and potency.

**α₂-Adrenoceptor agonists**

α₂-Adrenoceptors are expressed on human breast cancer cell lines and stimulation of these receptors is associated with increased proliferation. Clonidine has been shown to modulate NK cell activity and to enhance cellular proliferation in vitro and in vivo.

**Effect of opioids on host immune function and cancer**

Opioids are frequently prescribed for cancer patients for the management of acute postoperative pain and for chronic pain. In addition to their analgesic effects, opioids have well-established immunomodulatory effects. Evidence from experimental studies in cancer is conflicting. This is further complicated by the fact that the type of opioid, route, and duration of administration might all be relevant confounding factors.

Inflammatory cytokines have been shown to regulate the expression of the μ-opioid receptor (MOR) gene, highlighting an interaction between the opioid and immune systems. Opioids inhibit components of both cell-mediated and humoral immunity. However, all opioids do not suppress immune function to the same degree. Morphine has been demonstrated to decrease toll-like receptor (TLR) expression on macrophages by direct stimulation of the MOR in an animal model.

Fentanyl (40 μg kg⁻¹) 1 h before a laparotomy was shown to depress NK cell function in a rat model. A rapid increase in NK cell activity was seen during the first 24 h, but this was followed by significantly decreased activity, only returning to baseline activity levels after 8 days.

It is theorized that activation of specific genes during the perioperative period can contribute to cancer recurrence and metastasis. The NET1 gene has been shown to promote migration in adenocarcinoma cell lines. Breast cancer cells (both ER-positive and ER-negative) were shown to express MOR and morphine not only increased cancer cell migration, it also induced higher levels of the NET1 gene, known to promote adenocarcinoma, which seemed to mediate its increased migration effect.

**Effect of opioids on tumour development**

It has been proposed that opioids exert their effects on tumour growth by direct stimulation of the MOR; however,
there are also suggestions that these effects are mediated through activation of VEGF receptors. However, as yet, clinical evidence is unclear. Extended exposure to high concentrations of opioids can suppress tumour growth whereas a single-dose or low-dose opioid can promote tumour growth.55

The MOR is over-expressed in several types of non-small cell lung cancer. Silencing the MOR, using a knockout technique, significantly reduced opioid-induced tumour growth (35–50%) and metastasis (45–70%) in vitro.56 Treatment with methylnaltrexone (MNTX), a selective peripheral MOR-antagonist, produced similar effects. Tumour development was not observed in MOR-knockout mice 12 weeks after inoculation with lung cancer cells, suggesting that MOR may be involved in tumour development in the absence of an exogenous MOR agonist. A continuous infusion of MNTX for 2 weeks after visible tumour formation significantly reduced tumour growth and lung metastasis, and over-expression of MOR in human bronchoalveolar carcinoma cells increased the rate of lung metastasis 20-fold in a mouse model.57

These studies suggest that a direct link may exist between the MOR and lung cancer and this could have therapeutic potential. Singleton and Moss58 demonstrated that morphine stimulates tumour cell migration and proliferation in human endothelial cells in vitro. This effect was associated with activation of VEGF receptors and enhanced angiogenesis. Morphine was also associated with increased secretion of urokinase plasminogen activator, a promoter of tumour invasion and metastasis, in a breast cancer cell line. Of interest, no direct proliferative effect on the breast cancer cells was observed.59 MORs have been demonstrated in the nuclei of human colon cancer cells. Exposure of these cells to morphine, at a concentration of 0.1 μM for 24 h, was associated with a significant increase in secretion of urokinase plasminogen activator, suggesting a potential association between morphine and the invasive properties of the tumour.60

However, opioids can also paradoxically suppress tumour migration and proliferation in limited circumstances. In an experimental model of breast cancer, morphine inhibited cancer-promoting MMP-2 and MMP-9 production in a dose-dependent manner, mediated by the nitric oxide (NO) system.61 Some studies have shown that morphine lowers MMP-9, increases the MMP inhibitors TIMP-1 and -2 or both in co-cultured breast cancer and macrophages or endothelial cells. Morphine has been associated with inhibition of the adhesion and migration of colon cancer cells in vitro. In addition, an inhibitory effect on MMP production by the tumour cells was also observed.61

Opioids also tend to induce apoptosis in cancer cells through the NO pathway with activation of nuclear factor (NF)-κB, a potent transcription factor in the regulation of inflammation and apoptosis.62 Morphine, at clinically relevant doses, was shown to induce apoptosis in lung carcinoma and in promyelocytic leukaemia cell lines in vitro.63

Effect of opioids on angiogenesis
Singleton and Moss observed that opioid-stimulated angiogenesis could be reversed by MNTX directly through inhibition of the MOR. MOR inhibition resulted in reciprocal inhibition of VEGF receptors. This group also demonstrated a synergistic effect between MNTX and other chemotherapeutic agents, such as 5-fluorouracil and bevacizumab.64 This could potentially reduce the required therapeutic dose of these cytotoxic agents and consequently reduce unwanted side-effects.

Mechanisms proposed to explain the effect of morphine on angiogenesis include upregulation of COX-2 and increased PGE2 production.65 Nonetheless, chronic high-dose morphine inhibited angiogenesis in an animal model of lung cancer. VEGF secretion was reduced by 50% under hypoxic conditions and tumour progression reduced significantly, an effect attributed to attenuated angiogenesis. Differences in morphine dose and route of administration, different tumour cell lines and the effect of withdrawal or tolerance have been proposed as an explanation for these discrepancies.66

Effects of endogenous opioids
β-Endorphin is an endogenous opioid that affects the physiological stress response. Enhanced endogenous β-endorphin production increases NK cell cytotoxicity and anti-inflammatory cytokines and decreased pro-inflammatory cytokines (TNF-α). Perhaps the anti-neoplastic properties of β-endorphin are related to attenuation of the stress response. β-Endorphin has been suggested as a potential therapeutic cancer agent.67

A specific polymorphism of the MOR gene (A118G) might be associated with improved cancer survival rates at 10 yr. This study included more than 2000 female patients with breast cancer. Patients with invasive cancer who had one or more G alleles had a significantly decreased mortality rate at 10 yr.68 A number of confounding factors in this study should be considered, including the use of strong opioids, ongoing chemotherapy, and perception of pain.69

Effect of pain
The implications of inadequately controlled pain on the stress response should be considered if future strategies seek to limit opioids peripherally. Opioid analgesia and intrathecal bupivacaine significantly decreased postoperative LTR compared with no analgesia in a live animal model of breast cancer, demonstrating that effective perioperative analgesia can play a role in facilitating resistance to metastatic progression.

Role of cyclo-oxygenase (COX) inhibitors and prostaglandins in immunomodulation and promotion of tumour growth
Prostaglandins (PGs) are derived from arachidonic acid, which is converted to PGs by one of the two types of COX: COX-1 is a
Table 2 Summary of retrospective clinical evidence of effects of regional anaesthesia and cancer recurrence. PVAAs, paravertebral anaesthesia and analgesia

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Reference</th>
<th>Surgery</th>
<th>Technique</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>Exadaktylos et al. 2006&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Mastectomy and axillary clearance for breast cancer</td>
<td>GA+PVAA (n=50)</td>
<td>4-fold decrease in cancer recurrence in PVAAs group 2.5–4 yr follow-up</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Biki et al. 2008&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Radical prostatectomy for prostate carcinoma</td>
<td>GA+thoracic epidural group (n=102)</td>
<td>57% reduction in cancer recurrence in epidural group, P=0.012</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Wuethrich et al. 2010&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Radical prostatectomy for localized prostate carcinoma</td>
<td>GA+thoracic epidural (n=103)</td>
<td>Increase in clinical progression-free survival (P=0.009) in epidural group</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Ishmail et al. 2011&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Brachytherapy for cervical cancer</td>
<td>Neuraxial anaesthesia (n=69)</td>
<td>No difference in tumour recurrence (P=0.526) or survival (P=0.537)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Gottschalk et al. 2010&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Open colectomy</td>
<td>GA+epidural group (n=256)</td>
<td>No difference in cancer recurrence except in patients &gt;64 yr Follow-up 1.8 yr</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Gupta et al. 2011&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Open colectomy</td>
<td>GA+epidural (n=562)</td>
<td>GA+opioid group had higher mortality rate in rectal cancer (P=0.049)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Lin et al. 2011&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Laparotomy for ovarian carcinoma</td>
<td>Epidural anaesthesia + analgesia (n=106)</td>
<td>Epidural group had improved 3 yr and 5 yr survival rates (P=0.043)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>De Oliveira et al. 2011&lt;sup&gt;63&lt;/sup&gt;</td>
<td>‘Debulking’ surgery for ovarian cancer</td>
<td>Epidural (n=55)</td>
<td>Intraoperative epidural analgesia associated with reduced risk of cancer recurrence</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Lai et al. 2012&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Radiofrequency ablation of hepatocellular carcinoma</td>
<td>Epidural or GA hazard ratio for disease-free survival=3.66, P=0.001</td>
<td>GA associated with increased recurrence-free survival</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Day et al. 2012&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Laparoscopic colorectal resection for adenocarcinoma</td>
<td>Epidural (n=07)</td>
<td>No difference in overall survival (P=0.622) or disease-free survival at 5 yr (P=0.490)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Gottschalk et al. 2012&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Lymph node dissection for malignant melanoma</td>
<td>Spinal anaesthesia (n=52)</td>
<td>Non-significant trend towards improved cumulative survival rate in spinal anaesthesia group (P=0.087)</td>
</tr>
<tr>
<td>RCT (follow-up)</td>
<td>Christopherson et al. 2008&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Open colectomy for colorectal cancer</td>
<td>GA+epidural analgesia (n=85)</td>
<td>Early survival benefit (for up to 1.46 yr) in epidural group (P=0.012)</td>
</tr>
</tbody>
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Continued
constitutive enzyme, whereas COX-2 is expressed during inflammation and is induced by cytokines and growth factors. PGs activate the inflammatory response and are believed to promote cancer cell adhesion, migration, and invasion, inducing a response that favours neoplasia.69 PGs can directly influence immune function by inhibiting the activity of cytotoxic T cells and dendritic cells, down-regulating the anti-neoplastic cytokines, TNF-α and INF-γ and up-regulating the immunosuppressive cytokines 1L-10, 1L-4 and 1L-6.70 The activity of COX can also convert pro-carcinogens to carcinogens which induce mutagenesis and initiate tumour formation.71 Over-expression of COX-2 and increased production of PGE2 have been observed in a range of cancers of epithelial origin, including colorectal, breast, bladder, cervical, and ovarian. Given this trend, it is plausible that inhibition of PG synthesis using COX inhibitors might reduce progression of cancer.

There is epidemiological evidence that the long-term use of COX inhibitors reduces the risk of cancer, in particular, breast, colon, lung, and prostate cancer.72 A standard daily dose of celecoxib, a selective COX-2 inhibitor, was associated with a 69% risk reduction in a case–control study of patients with colorectal cancer.73 A recent prospective cohort study with over 2.5 million patient-years of follow-up over 10 years demonstrated that the use of any COX inhibitor was associated with a 20% reduced risk of colorectal cancer.72

COX-2 is frequently over-expressed in breast cancer and PGE2 is believed to contribute its metastatic potential. A meta-analysis of the effects of aspirin and ibuprofen on >520 000 patients demonstrated that they were associated with decreased risk of developing breast cancer.74 However, the prolonged use of specific COX-2 inhibitors can cause cardiovascular morbidity.75 In the absence of a prospective, randomized trial, it is impossible to state whether perioperative COX inhibition can affect cancer recurrence rates.

### Regional anaesthesia

Regional anaesthesia attenuates the neuroendocrine stress response, reducing opioid, and intraoperative volatile anaesthetic agent requirements.76 This combination of effects might allow enhanced preservation of perioperative immune function and possibly reduce the incidence of cancer recurrence. Addition of spinal to GA reduced lung metastasis following laparotomy compared with GA alone.77 Another study reported similar results that spinal anaesthesia was associated with preservation of NK cell function in vitro.22 However, a recent meta-analysis found no association between regional anaesthesia and the preservation of NK T-lymphocyte function after operation when compared with GA.12

Small prospective clinical studies randomized patients undergoing breast cancer surgery to receive either GA with propofol, in addition to continuous paravertebral anaesthesia and analgesia (PVA), or GA with sevoflurane and opioid analgesia. While propofol with continuous PVA attenuated the stress response, no difference in VEGF and PGE2 concentrations was observed.10 But serum from patients randomized to propofol–PVA, as a putative ‘anti-cancer’ anaesthetic, showed greater inhibitory effects on oestrogen receptor-negative breast cancer cell function than the serum of patients who had received standard GA.78

A long-term follow-up analysis of the MASTER trial, a multicentre prospective clinical study in which patients undergoing major abdominal surgery were randomized to receive either GA with either epidural or opioid analgesia found no difference in cancer-free survival between the groups. The median time to cancer recurrence or death was 2.6 yr in the epidural group, when compared with 2.8 yr in the opioid group. This was the first long-term follow-up of patients prospectively randomly assigned to either opioid or epidural analgesia. A potential confounding factor might have been the amount of volatile anaesthesia required intraoperatively, which was

### Table 2 Continued

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<thead>
<tr>
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<th>Technique</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (follow-up)</td>
<td>Tsui et al. 201098</td>
<td>Radical prostatectomy</td>
<td>GA+epidural analgesia (n=49)</td>
<td>No difference in disease-free survival (P=0.44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GA+opioid analgesia (n=50)</td>
<td>4.5 yr follow-up</td>
</tr>
<tr>
<td>RCT (follow-up)</td>
<td>Myles et al. 201179</td>
<td>Major abdominal surgery, subgroup analysis of patients with colorectal cancer</td>
<td>GA+epidural analgesia (n=230)</td>
<td>No difference in cancer recurrence (P=0.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GA+opioid analgesia (n=216)</td>
<td>or recurrence-free survival (P=0.61)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Cummings et al. 201279</td>
<td>Open colectomy for non-metastatic colorectal cancer</td>
<td>Epidural analgesia (n=9670)</td>
<td>Recurrence and mortality rates at 5 yr also similar</td>
</tr>
<tr>
<td>population</td>
<td></td>
<td></td>
<td>Opioid pain management n=32 481</td>
<td>61% 5-yr survival with epidural vs 55% opioid (P&lt;0.001)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>No difference in cancer recurrence rates (P=0.28)</td>
</tr>
</tbody>
</table>
not recorded in the original MASTER trial. While the study was well powered to detect a one-third risk reduction, smaller but clinically significant effects might have been overlooked. Of note, older age, female gender, tumour node metastasis status, and allogenic red blood cell transfusion were all associated with reduced cancer-free survival.\textsuperscript{79}

**Effect of allogeneic blood transfusion**

Allogenic blood transfusion is associated with modulation of the immune system and might also be associated with increased risk of cancer recurrence, perioperative infections, and mortality.\textsuperscript{80} Transfused leucocytes can be involved in transfusion-related immunomodulation, leading to alterations in circulating lymphocytes, helper T-cell, suppressor T-cell ratios, and B-cell function. Irradiated or leucocyte-depleted red cells are frequently administered to cancer patients, but an association between patients who received leucocyte-depleted red cells and significantly decreased disease-free survival and overall survival, compared with patients who did not receive a transfusion has been observed.\textsuperscript{81} A recent meta-analysis examined the effect of transfusion on cancer recurrence, disease-free survival, and overall survival in patients undergoing surgery for resection of lung cancer in 5378 patients. No definitive conclusions could be established; however, there appeared to be an association between transfusion and reduction of disease-free survival.\textsuperscript{82}

**Effect of psychological stress on cancer recurrence**

Up to 30% of women with breast cancer suffer from anxiety and depression, and a history of depression might predict cancer recurrence and overall survival.\textsuperscript{83} The psychological stress and anxiety endured perioperatively stimulates the physiological stress response through the HPA axis and the sympathetic nervous system. This leads to secretion of glucocorticoids, endogenous opioids, and catecholamines, which exerts a significant impact on the tumour microenvironment. It is proposed that \(\beta\)-adrenoreceptor antagonists might inhibit some of the deleterious effects of stress.

Women who were taking the non-selective \(\beta\)-antagonist propranolol during the year before the diagnosis of breast cancer were less likely to have local tumour invasion at presentation and had a lower incidence of cancer-related mortality compared with women who did not. This effect was not observed in patients taking the selective \(\beta_1\)-antagonist atenolol, but the small numbers of women in the propranolol cohort and the retrospective data indicate that these results should be interpreted cautiously.\textsuperscript{84}

**Effect of perioperative hypothermia on cancer recurrence**

Inadvertent perioperative hypothermia is experienced by up to 70% of patients under anaesthesia as a result of cool ambient theatre temperature, blunted thermoregulation as

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**Table 3** The future: summary of some ongoing prospective, randomized, clinical trials by Outcomes Research Consortium, Cleveland, OH

<table>
<thead>
<tr>
<th>Title</th>
<th>Study design</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>Location</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional anaesthesia and breast cancer recurrence, NCT00418457</td>
<td>Multi-centre prospective randomized clinical trial, (n = 1100)</td>
<td>GA + postoperative opioid analgesia or GA or deep sedation with epidural or paravertebral anaesthesia</td>
<td>Cancer recurrence rate up to 10 yr</td>
<td>Mater University Hospital, Ireland; Cleveland Clinic, OH, USA, Medical University of Vienna, Austria; University of Dusseldorf, Germany</td>
<td>March 2015</td>
</tr>
<tr>
<td>The effect of adding intraoperative regional anaesthesia on cancer recurrence in patients undergoing lung cancer resection, NCT011799308</td>
<td>Prospective, randomized, double-blind trial, (n = 1532)</td>
<td>GA + thoracic epidural analgesia or GA + postoperative opioid analgesia or GA + thoracic epidural analgesia</td>
<td>Disease-free survival up to 5 yr</td>
<td>Cleveland Clinic, OH, USA, Mater University Hospital, Ireland</td>
<td>August 2018</td>
</tr>
<tr>
<td>Regional anaesthesia in colon rectal surgery, NCT00684229</td>
<td>Multi-centre, prospective, randomized, double-blind trial, (n = 2500)</td>
<td>GA (sevoflurane) + opioid analgesia or GA + epidural anaesthesia</td>
<td>Cancer recurrence rate up to 5 yr</td>
<td>Cleveland Clinic, OH, USA, Hospital Italiano de Buenos Aires, Argentina; University of Dusseldorf, Germany</td>
<td>December 2022</td>
</tr>
</tbody>
</table>
a result of anaesthesia and convective air streams in theatre. Hypothermia induces changes at a cellular level that negatively impact innate and adaptive immunity. Incubation of human monocytes from healthy volunteers at 34°C for 4 h was associated with inhibition of antigen presentation as assessed by HLA-DR expression. Cytokine secretion was also decreased. A recent cohort study assessed the effect of hypothermia (<36°C) in patients with advanced ovarian cancer undergoing debulking surgery. Hypothermia was associated with a significantly reduced overall survival, at 34 months compared with 45 months.

## Retrospective clinical evidence of an association between regional anaesthesia and cancer recurrence

There have been a number of retrospective analyses regarding the implications of regional anaesthesia during cancer surgery for a variety of tumours on recurrence, metastases, and survival, which have yielded conflicting evidence. These are summarized, together with follow-up analysis of some previous randomized, controlled trials (FARCTs) designed to evaluate non-cancer outcomes, in Table 2. A recent large-scale database study found that the use of epidural analgesia with GA during colorectal cancer surgery was associated with improved 5 yr survival (61 vs 56% for patients who had GA only), but not with any difference in cancer recurrence as assessed by referral for chemotherapy or radiotherapy. Perhaps the effect of regional anaesthesia is tumour-specific; however, discrepancies remain. Retrospective studies are inherently susceptible to selection bias and are useful only to highlight associations and generate hypotheses. Only prospective, multicentre, randomized, controlled trials can confirm a causal link, and these are ongoing in a number of tumour types, which are summarized in Table 3.

## Conclusion

Some, but not all, experimental, animal and retrospective clinical evidence indicate an association between anaesthetic technique and cancer recurrence, but only prospective, randomized, clinical trials can prove a causal link. These are ongoing, randomizing patients with primary cancer to receive an ‘anti-cancer’ anaesthetic technique (consisting of regional anaesthesia with propofol based GA) or standard GA with opioid analgesia, and the results are eagerly awaited; this will take a further 3–7 yr. Meanwhile, there is no evidence to support altering current routine clinical anaesthetic practice in cancer patients undergoing surgery.

## Declaration of interest

D. J. B. is a member of the Editorial Board of the BJA.

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