Regional anaesthesia and analgesia: relationship to cancer recurrence and survival

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Abstract
Cancer treatment is associated with significant morbidity and mortality. Surgery is a mainstay of treatment for many tumours, and anaesthetists care for cancer patients on a daily basis. Surgery itself induces a stress response and inhibits the immune system, and cancer surgery is associated with the release of tumour cells systemically. Preclinical and clinical studies suggest that the anaesthetics and adjuvants given in the perioperative period can affect cancer recurrence and survival, perhaps tipping the balance in some instances to determine whether cancer progresses or regresses. Retrospective studies have hinted that regional anaesthesia can play a protective role in cancer surgery, but many of these studies are small and subject to bias. We eagerly await the results of several large, randomized controlled trials examining the impact of regional anaesthesia and analgesia on cancer recurrence and survival.

Key words: anaesthesia, conduction; anaesthetics, local; anaesthetics, inhalation; cancer; opioid

Editor’s key points
- Considerable evidence suggests that anaesthesia can have both direct and indirect effects on cancer cell survival and metastasis.
- Small retrospective clinical trials suggest that regional anaesthesia is associated with improved survival in cancer surgery.
- Large randomized clinical trials comparing the effects of regional and general anaesthesia on long-term outcome after cancer surgery are necessary to guide clinical practice.

Cancer and the immune system
In order to understand how surgery and anaesthesia affect cancer recurrence and survival, one first needs to understand the basics of cancer biology. The tumour microenvironment consists of cancer cells and various inflammatory cells and mediators. Both tumour and inflammatory cells secrete a complex array of chemical and protein signalling molecules that act in both an autocrine and a paracrine manner to influence cancer growth and metastasis. A tumour can be viewed as an organism unto itself, and establishes an intricate physical and chemical relationship with the body and the immune system. Many of the molecular and cellular mechanisms underlying this process remain to be elucidated fully.
It has long been recognized that cancer can occur at sites of inflammation and injury, and it is now known that inflammatory cells and mediators play a key role in cancer formation and progression. Cancer can form in the setting of DNA damage and somatic alterations. These changes have been termed ‘initiation’ and can persist in cells indefinitely until a second injury or ‘promotion’ occurs. Promotion can be caused by inflammation, injury, irritants or a host of other exposures. Promotion results in recruitment of inflammatory cells, release of chemical mediators, and oxidative damage, and ultimately, a failure of apoptosis that results in undeterred cellular proliferation. Angiogenesis is required for tumour growth and metastasis formation and is the process by which new vessels form from existing endothelial cells. Angiogenesis normally happens in response to injury and inflammation and is characterized by the degradation and remodelling of the extracellular matrix and the proliferation and migration of endothelial cells. Angiogenesis is critical to the survival of tumours, and thus has been the target of many recent treatments for cancer.

The immune system plays a key role in both the progression and the regression of cancer cells. The immune system can be divided into the innate and the adaptive systems. The innate system is made up of epithelial barriers, granulocytes, macrophages, natural killer (NK) cells, and dendritic cells. This system is the first line of defence against invading organisms and tumour cells. The adaptive immune system serves to eliminate threats of many recent treatments for cancer.

**Fig 1** The complex interplay between cancer cells, the immune system, and anaesthetic agents. NSAIDs, non-steroidal anti-inflammatory drugs.
Transforming growth factor-β is a cytokine involved in cell growth, differentiation, and other functions. In normal cells it halts proliferation, promotes differentiation, and induces apoptosis. In many types of cancer, portions of the TGF-β signalling pathway malfunction, causing loss of control over cellular proliferation. It can also be a stimulator of angiogenesis in vivo.1,7

Prostaglandin E2 (PGE2) is a key mediator of the immune system in both chronic infection and cancer. Prostaglandins are derived from arachidonic acid by cyclooxygenases (COX) 1 and 2 and by prostaglandin synthases. Many cancers have elevated concentrations of COX2 and overproduce prostaglandins. Prostaglandin E2 is crucial to inflammation and phagocyte-mediated immunity, and to limiting the potentially harmful activation of cytotoxic cells.8 Prostaglandin E2 plays an important role in promoting cancer progression by inhibiting apoptosis, stimulating angiogenesis, and enhancing invasion.9

Surgery and the stress response

Surgical resection is a mainstay of cancer treatment for many tumour types. There is increasing evidence that primary tumour excision can hasten metastasis in some patients by triggering cancer dissemination and growth.10–14 Circulating tumour cells can be dormant for long periods of time. One study of former, clinically disease-free, breast cancer patients demonstrated that 59% had circulating tumour cells 7–22 yr after mastectomy.15 These cells live for only a few hours, so they must be continually replenished by a source. Tumours are contained within the chemical and hormonal milieu of the body, and communicate with it through complex cellular signals. Primary tumours secrete both inducers and inhibitors that can influence circulating tumour cells. Once the primary tumour is removed, the balance of inducers to inhibitors can potentially be disrupted, leading to activation of the circulating tumour cells and metastasis.16 All of this is occurring under the watchful eye of the immune system. It is suspected that cancer cells are not only able to evade the body’s defenses, but are also able to communicate with and modulate the immune system.

Surgery has long been known to suppress the immune system. This often follows an elevated production of stress hormones and a dramatic inflammatory response.16,17 Pro-inflammatory cytokine concentrations and the duration of their elevation have been shown to be correlated with surgical insult, lasting as long as 3–5 days after surgery.17 Both experimental and clinical studies have shown that surgery inhibits T-cell, B-cell, and NK-cell function for days after a surgical insult.17

Natural killer cells, in particular, are known to play an important role in tumour development and metastatic spread.18 In humans, NK-cell activity is correlated with susceptibility to multiple types of cancer.19 In an elegant study, Melamed and colleagues20 demonstrated that surgery results in decreased NK-cell activity and increased metastasis, and that blocking the stress and inflammatory responses associated with surgery reverses these effects. In laparatomized rats, surgery significantly decreased NK-cell activity and increased lung tumour retention and lung metastasis after i.v. inoculation with MABD106 cancer cells compared with non-operated, anaesthetized control rats. MABD106 is a mammary adenocarcinoma cell line that metastasizes only to the lungs. Administration of a β-receptor antagonist (nadolol), a prostaglandin synthesis inhibitor (indomethacin), or both dramatically reduced the effects on lung tumour retention, metastasis, and NK-cell activity. The effect of co-administration was greater than the effect of each administered alone. In addition, administration of clinically relevant doses of a β-receptor agonist (metaproterenol), a prostaglandin (PGE2), or both promoted metastasis of tumour cells. The effect of co-administration was additive.

Some of the effects of surgery on the stress response and immune function in the perioperative period are likely to be mediated by pain. Pain has been shown to activate the stress response and suppress the immune system in both animals and humans.21 Medications that reduce pain, decrease the inflammatory response, or both, such as morphine, fentanyl, and non-steroidal inflammatory drugs (NSAIDs), have been shown to decrease the potential for metastasis in rats and humans.22–24

Many of the effects of surgery on pain and the stress response can be reduced dramatically by regional anesthesia. It is important to note that some elements of the stress response are more difficult to block than others. For example, in infants undergoing heart surgery the dose of fentanyl required to produce analgesia (1–5 μg kg⁻¹) is less than that required for haemodynamic stability (5–10 μg kg⁻¹), which is less than that required to prevent increases in glucose, cortisol, and catecholamine concentrations (25–50 μg kg⁻¹).16,25 Regional anesthesia, especially with dense block, has the benefit of being able to markedly reduce or eliminate the surgical stimulus. Studies in heart and abdominal surgery patients have shown that the addition of intraoperative epidural analgesia to general anesthesia results in reduced plasma concentrations of cortisol, β-endorphin, and epinephrine.26,27 In abdominal surgery patients, intraoperative epidural analgesia was also associated with higher numbers of lymphocytes and T-helper cells, preserved interferon-γ concentrations, and a beneficial effect on the ratio of Th1/Th2 cytokines.28 Spinal anesthesia has also been shown to preserve the Th1/Th2 cytokine ratio in rats undergoing laparotomy, which paralleled its ability to decrease liver metastasis.29

In 2001, Bar-Yosef and colleagues30 hypothesized that the addition of spinal to general anesthesia would result in less immunosuppression and reduced lung metastases in rats inoculated with MABD106 cancer cells. Anaesthetized, non-laparatomized rats were compared with control rats and with laparatomized rats receiving three different anaesthesia regimens: halothane alone, halothane with morphine i.v., and halothane with spinal anesthesia. No significant difference in the number of lung metastases existed between the subgroups of anaesthesia without surgical intervention. Surgery with halothane anesthesia increased the number of metastases two-fold compared with control and anaesthesia-only rats. The addition of spinal block to halothane anesthesia reversed this, whereas morphine i.v. had no significant effect. Both surgery and anaesthesia decreased NK-cell activity. Neither spinal anaesthesia nor systemic morphine had a significant effect on NK activity.

Anaesthetic agents

General anaesthetic agents themselves are thought to suppress the immune system and promote cancer metastasis.30 Almost all anaesthetic agents have been shown to have a negative impact on various components of the immune system, such as inhibiting cell-mediated immunity or producing an alteration in the balance of pro-inflammatory and anti-inflammatory cytokines.31

Volatile anaesthetics appear to have a pronounced negative effect on immune function and cancer spread. Administration of halothane and isoflurane results in increased metastatic spread of melanoma,32 and halothane and nitrous oxide accelerate postoperative growth of lung cancer metastases in mice.33 Volatile agents can exert their influence on cancer cells via
several mechanisms. They have been shown in various studies to increase concentrations of VEGF and MMPs, known stimulators of angiogenesis, and to increase cancer cell migration in vitro.\textsuperscript{30} 34–37 In addition, volatile agents have been shown to upregulate hypoxia-inducible factors. These transcription factors are thought to mediate the protective effects of volatile agents on ischaemia–reperfusion injury, but have also been shown to be involved in increased tumorigenesis and metastasis by influencing angiogenesis, energy metabolism, cell proliferation, apoptosis, and cell migration.\textsuperscript{30} 37–39

In contrast to volatile agents, propofol seems to exhibit a beneficial effect in terms of reducing inflammatory cytokines, preserving NK-cell activity, and inhibiting cancer spread.\textsuperscript{40} 44 In addition, propofol has been shown to suppress the synthesis and activation of hypoxia-inducible factors.\textsuperscript{50} 44

Melamed and colleagues\textsuperscript{45} compared the effects of propofol, halothane, ketamine, and thiopental on NK-cell activity and metastatic spread of MADB106 tumour cells in rats. All anaesthetics reduced the number of NK cells, and all anaesthetics except propofol decreased NK-cell activity and increased lung metastases and tumour retention. Ketamine had the greatest effect, increasing metastases more than 2.5-fold. This increase was significantly reduced by pretreatment with the β-receptor antagonist nadolol, suggesting that stimulation of β2-adrenergic receptors might underlie the inhibitory effects of ketamine on NK-cell activity.

**Local anaesthetics**

Local anaesthetics themselves seem to be protective against tumour growth and metastasis. They appear to act via several mechanisms, including direct cytotoxicity and induction of apoptosis; inhibition of proliferation, migration, and invasion; and modulation of gene expression via methylation.\textsuperscript{45}

Local anaesthetics in high concentrations are known to be cytotoxic to neuronal cells;\textsuperscript{46} their toxicity seems to be correlated with lipid solubility and thus with potency.\textsuperscript{46} 47 Cytotoxicity includes cell death via necrosis or apoptosis. All local anaesthetics cause necrosis, but lidocaine and bupivacaine cause apoptosis in neuroblastoma cells\textsuperscript{48} and in breast and thyroid cancer cells.\textsuperscript{49} Apoptosis is controlled by a group of intracellular cytochrome proteases known as caspases. Chang and colleagues\textsuperscript{40} demonstrated that treatment of breast cancer cells with clinically relevant concentrations of lidocaine and bupivacaine induced caspases 7, 8, and 9, resulting in apoptosis and decreased cell viability. In addition, local anaesthetic injection into breast xenografts in mice resulted in evidence of apoptosis, including a higher expression of cleaved caspase 7 and increased byproducts of DNA fragmentation. In another study, this group showed that the treatment of thyroid cancer cells with lidocaine and bupivacaine induced apoptosis and that this effect was mediated by the mitogen-activated protein kinase pathway.\textsuperscript{49}

Local anaesthetics also inhibit cancer cell proliferation, migration, and invasion. Yoon and colleagues\textsuperscript{50} demonstrated that tetracaine and lidocaine inhibited the extension of microtubules and their ability to promote tumour cell aggregation and reattachment. Local anaesthetics can also influence proliferation and invasion via their effects on cell signalling pathways.\textsuperscript{51–54}

Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor with an important role in epithelial cell proliferation. Mutations of EGFR have been linked to several types of cancer.\textsuperscript{51} Epidermal growth factor receptor is activated via phosphorylation by the binding of specific ligands, including epidermal growth factor (EGF). Cancer cells express EGFR and EGFR-binding ligands. For example, the fibrosarcoma cell line HT1080 expresses heparin-binding epidermal growth factor-like growth factor (HB-EGF), which is shed from cancer cells and phosphorylates EGFR, leading to autoactivation and increased cell invasion. Mammamoto and colleagues\textsuperscript{52} demonstrated that lidocaine in clinically relevant concentrations decreased the invasive ability of HT1080 cells by inhibiting the shedding of HB-EGF. Sakaguchi and colleagues\textsuperscript{53} showed that lidocaine inhibited EGF stimulation of EGFR tyrosine kinase activity and inhibited both serum- and EGF-induced proliferation of tongue cancer cells.

Cell signalling pathways involving the Src tyrosine protein kinase and intercellular adhesion molecule-1 (ICAM-1) are also linked to tumour growth and metastasis. Src has been implicated in epithelial-to-mesenchymal transformation and decreased cell adhesion, resulting in metastasis. ICAM-1 is a cell surface receptor involved in leucocyte adhesion and is known to facilitate tumour growth and spread. Inflammation and TNF-α increase both the activation of Src and the expression of ICAM-1.\textsuperscript{54} Piegeler and colleagues\textsuperscript{55} demonstrated that amide local anaesthetics decreased TNF-α-induced Src activation and ICAM-1 phosphorylation in human lung cancer cells and inhibited cancer cell migration. These effects were independent of local anaesthetic sodium channel block.

Local anaesthetics can also inhibit cancer cell proliferation by effects on the modulation of gene expression via methylation of DNA. Transcriptional silencing of tumour suppressor genes caused by DNA hypermethylation occurs in many cancers. Lidocaine has been shown to demethylate DNA in breast cancer cell lines,\textsuperscript{56} and procaine has been shown to demethylate DNA and inhibit tumour growth in breast, hepatoma, and leukaemia cell lines.\textsuperscript{57–59}

Finally, many types of cancer, including breast, colon, and prostate, express local-anaesthetic-sensitive voltage-activated sodium channels.\textsuperscript{58}–62 Baptista-Hon and colleagues\textsuperscript{63} demonstrated that ropivacaine inhibits voltage-activated sodium channels in colon cancer cells and decreases cell invasion. Therefore, blockade of sodium channels might have direct inhibitory effects on cancer cells in addition to having beneficial effects in terms of the blockade of noxious stimuli.\textsuperscript{64}

**Opioids**

Opioid medications have long been thought to suppress the immune system. In 1984, Shavit and colleagues\textsuperscript{65} demonstrated that endogenous opioid-mediated footshock stress in rats resulted in suppression of NK-cell activity and that this effect was reversed by administration of naltrexone. Since that time, there has been considerable evidence to support the theory of opioid-mediated immune suppression, and additional evidence pointing to opioid-mediated enhancement of tumorigenesis and metastases. Counteracting this is literature suggesting that opioids do not suppress immune function or contribute to cancer spread.

Many studies of the effects of opioids on the promotion of cancer growth are in vitro studies or animal studies using i.v. inoculation of tumour cells or xenografts (tumours transplanted into syngeneic specimens). Gupta and colleagues\textsuperscript{66} demonstrated that morphine, like VEGF, stimulates endothelial cell proliferation through the mitogen-activated protein kinase/extracellular signal-regulated kinase signalling pathway, resulting in angiogenesis. Morphine additionally inhibited apoptosis and promoted cell-cycle progression in endothelial cells. Consistent with these in vitro results, morphine administration resulted in angiogenesis and tumour progression in a rat xenograft model.\textsuperscript{66} Likewise, Singleton and colleagues\textsuperscript{67} found that opioids...
induce VEGF receptor activation, resulting in endothelial cell migration (required for angiogenesis), and that this effect was inhibited by the peripherally acting opioid antagonist, methylnaltrexone.

Opioids might exert their effects directly by binding to opioid receptors on cancer cells themselves. Mathew and colleagues noted that there was a five- to 10-fold increase in μ opioid receptor (MOR) expression in lung tissue from patients with non-small cell lung carcinoma and in non-small cell lung carcinoma cell lines. Morphine and the MOR agonist d-Ala2-MePhe4-Glyol5 enkephalin increased in vitro growth of Lewis lung carcinoma. Cancer invasion and growth were inhibited up to 80% by silencing MOR expression in tumour cells or by the administration of methylnaltrexone. Additionally, injection of MOR-silenced Lewis lung carcinoma led to 65% fewer metastases, and mice lacking MORs showed no such reduction.

Regional anaesthesia and analgesia and cancer progression: clinical trials

Systematic reviews

Systematic reviews looking at the association between survival, cancer recurrence, or both and type of anaesthesia have generally found that current evidence is insufficient to draw any concrete conclusions regarding the benefit of regional anaesthesia (Table 1). These analyses have included patients undergoing abdominal, prostate, breast, gastroesophageal, laryngeal, ovarian, and cervical cancer surgeries. A Cochrane Review found the quality of the data examined to be low or very low, and the authors were unable to draw any conclusions. A recent large systematic review included 20 studies with more than 54 000 patients. The authors found perioperative regional anaesthesia to be associated with improved overall survival but not reduced cancer recurrence. Another large review compared the effect of epidural anaesthesia (with or without general anaesthesia) with general anaesthesia alone on survival and recurrence in cancer surgery. This systematic review included more than 46 000 patients and found an overall survival benefit in favour of epidural anaesthesia compared with general anaesthesia alone. An even greater benefit was seen in the colorectal subset of patients. No benefit of epidural anaesthesia was found for recurrence-free survival. Pei and colleagues found no overall benefit to combined epidural and general anaesthesia compared with general anaesthesia in terms of postoperative recurrence and metastasis, although there was a benefit in the subgroup of patients with prostate cancer and in those followed for ≤2 yr after surgery [odds ratio=0.66, 95% confidence interval (CI) 0.46–0.95, P=0.027; and OR=0.70, 95% CI 0.51–0.98, P=0.035, respectively].

As described below, most of these systematic reviews are small and retrospective in nature. Many were intended to be hypothesis generating. Large trials with thousands of patients and years of follow-up will be needed to identify true differences between anaesthetic regimens. Several randomized trials comparing regional anaesthesia and analgesia with general anaesthesia are currently recruiting patients undergoing surgery for breast cancer, colorectal cancer, malignant melanoma, and pancreatic cancer (NCT0014857, NCT00684229, NCT01588847, NCT01318161, and NCT01929915). Two of these (NCT0014857 and NCT00684229) are large, multicentre trials.

If benefit is found for regional anaesthesia in terms of cancer recurrence in large, well-conducted clinical trials, it might still be difficult to tease out what part of that benefit is directly attributable to the regional anaesthetic itself and what part is related to avoidance of other perioperative factors associated with cancer progression, such as pain, the stress response, volatile anaesthetics, and opioids.

Non-steroidal anti-inflammatory drugs

Animal and human studies have shown a clear benefit for NSAIDs in the prevention of cancer. These drugs inhibit the activity of cyclooxygenase, which plays an important role in the formation of prostaglandins. Concentrations of COX2 are up-regulated in various forms of cancer, including breast, lung, prostate, stomach, pancreas, and bladder cancer. One product of COX2 is PGE2, which is pro-inflammatory and is associated with cancer progression. Some of the effects of PGE2 on cancer cells include enhancement of migration and invasion via activation of EGFR and promotion of angiogenesis.

Apart from primary prevention, NSAIDs appear to reverse the cancer-promoting effects of surgery and opioids. Administration of indomethacin dramatically reduced the increase in lung metastases and tumour retention produced by surgery in rats inoculated with mammary adenocarcinoma. Farooqui and colleagues studied i.v. inoculation of a highly invasive form of breast cancer in mice. Two weeks of morphine treatment stimulated COX2 and PGE2 production, stimulated angiogenesis, increased metastasis of breast tumours, and decreased survival in mice. Administration of celecoxib reversed these effects. In a retrospective study of 327 breast cancer patients undergoing mastectomy with axillary dissection, ketorolac administration before surgery was associated with a lower rate of cancer recurrence, while the analgesics sufentanil, ketamine, and clonidine showed no such reduction.

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Table 1 Summary of studies examining regional anaesthesia and cancer recurrence. BCR, biochemical recurrence; CI, confidence interval; met, metastasis; GA, general anaesthesia; NR, not reported; OR, overall recurrence; OS, overall survival; PFS, progression-free survival; RA, regional anaesthesia and analgesia; RC, retrospective cohort; RFS, recurrence-free survival; RR, relative risk; SA of RCT, secondary analysis of randomized controlled trial; SR, systematic review; TTP, time to tumour progression; TTR, time to recurrence

<table>
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<tr>
<th>Study</th>
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<th>RA/GA</th>
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<th>End points</th>
<th>Hazard ratio</th>
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<td>Cakmakkaya and colleagues&lt;sup&gt;80&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>OS</td>
<td>0.84</td>
<td>0.74–0.96</td>
<td>+</td>
</tr>
<tr>
<td>Cummings and colleagues&lt;sup&gt;91&lt;/sup&gt;</td>
<td>RC</td>
<td>9278/40377</td>
<td>Open colectomy</td>
<td>OS</td>
<td>0.84</td>
<td>0.75–0.94</td>
<td>+</td>
</tr>
<tr>
<td></td>
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<td>RFS</td>
<td>0.88</td>
<td>0.64–1.22</td>
<td>–</td>
</tr>
<tr>
<td>Myles and colleagues&lt;sup&gt;92&lt;/sup&gt;</td>
<td>SA of RCT</td>
<td>230/216</td>
<td>Major abdominal surgery</td>
<td>OS</td>
<td>0.84</td>
<td>0.75–0.94</td>
<td>+</td>
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<td>RFS</td>
<td>0.88</td>
<td>0.64–1.22</td>
<td>–</td>
</tr>
<tr>
<td>Christopherson and colleagues&lt;sup&gt;93&lt;/sup&gt;</td>
<td>SA of RCT</td>
<td>85/92</td>
<td>Open colectomy</td>
<td>OS (non-metastic, &lt;1.46 yr)</td>
<td>0.22</td>
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<td>0.70</td>
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<tr>
<td>Holler and colleagues&lt;sup&gt;94&lt;/sup&gt;</td>
<td>RC</td>
<td>442/307</td>
<td>Laparoscopic colorectal</td>
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<td>0.73</td>
<td>0.43–1.27</td>
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<td>OS (colon)</td>
<td>0.82</td>
<td>0.40–1.75</td>
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<td>Gupta and colleagues&lt;sup&gt;95&lt;/sup&gt;</td>
<td>RC</td>
<td>562/93</td>
<td>Open colorectal</td>
<td>OS</td>
<td>0.73</td>
<td>0.43–1.27</td>
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<td>0.82</td>
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<td>RC</td>
<td>256/253</td>
<td>Open colorectal</td>
<td>OS</td>
<td>0.73</td>
<td>0.43–1.27</td>
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<td>Day and colleagues&lt;sup&gt;97&lt;/sup&gt;</td>
<td>RC</td>
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<td>OS</td>
<td>0.73</td>
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<td>0.82</td>
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<tr>
<td>Merquiol and colleagues&lt;sup&gt;98&lt;/sup&gt;</td>
<td>RC</td>
<td>111/160</td>
<td>Laryngectomy and pharyngolaryngectomy</td>
<td>OS</td>
<td>0.61</td>
<td>0.39–0.96</td>
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<td>0.39–0.96</td>
<td>+</td>
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<tr>
<td>Schlagenhauff and colleagues&lt;sup&gt;99&lt;/sup&gt;</td>
<td>RC</td>
<td>2185/2136</td>
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<td>OS</td>
<td>0.95</td>
<td>0.76–1.17</td>
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<td>OS (metastatic)</td>
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<td>0.76–1.17</td>
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<td>RC</td>
<td>52/221</td>
<td>Open colorectal</td>
<td>OS</td>
<td>0.95</td>
<td>0.76–1.17</td>
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<td>0.95</td>
<td>0.76–1.17</td>
<td>–</td>
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<tr>
<td>Lin and colleagues&lt;sup&gt;101&lt;/sup&gt;</td>
<td>RC</td>
<td>106/37</td>
<td>Complete cytoreduction for ovarian cancer</td>
<td>RR of death</td>
<td>NR, RR for GA=1.46</td>
<td>1.21–1.76</td>
<td>+</td>
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<td>OS</td>
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<td>0.70–0.96</td>
<td>+</td>
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<tr>
<td>De Oliveira and colleagues&lt;sup&gt;102&lt;/sup&gt;</td>
<td>RC</td>
<td>55/127</td>
<td>Laparotomy for ovarian cancer, debulking</td>
<td>OS</td>
<td>0.82</td>
<td>0.70–0.96</td>
<td>+</td>
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<td>0.70–0.96</td>
<td>+</td>
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<td>Capmas and colleagues&lt;sup&gt;103&lt;/sup&gt;</td>
<td>RC</td>
<td>47/47</td>
<td>Local RFS</td>
<td>OS</td>
<td>0.82</td>
<td>0.70–0.96</td>
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<td>0.82</td>
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Breast cancer

One of the first studies to examine the question of whether anaesthesia can affect outcome in breast cancer patients was a retrospective review by Exadaktylos and colleagues.\(^\text{[109]}\) This study included 129 patients undergoing mastectomy with axillary dissection, 50 of whom received paravertebral block and general anaesthesia followed by paravertebral infusion for 48 h, and 79 of whom received general anaesthesia alone followed by morphine patient-controlled analgesia. There were no significant differences between groups in terms of patient characteristics, surgical details, tumour presentation, or prognostic factors. The authors found a significant difference favouring paravertebral anaesthesia and analgesia, with a recurrence and metastasis-free survival rate of 94% (95% CI 87–100%) vs 82% (95% CI 74–91%) at 24 months and 94% (95% CI 87–100%) vs 77% (95% CI 68–87%) at 36 months after surgery.

In order to provide a more adequate answer to the question of whether regional anaesthesia and analgesia can impact breast cancer recurrence, a large, multicentre international trial is being conducted in patients with Stage 1 breast cancer undergoing mastectomy with or without axillary dissection (NCT00418457).\(^\text{[104]}\) One thousand one hundred patients are to be enrolled during 5 yr and will be randomized to a regional anaesthetic technique (thoracic epidural or paravertebral block) with propofol sedation and postoperative regional infusion or to general anaesthesia with sevoflurane and postoperative morphine patient-controlled analgesia. The primary end point will be cancer recurrence.

Although we will not have definitive results from trial NCT00418457 for many years, results from in vitro studies performed on tissue and serum samples from patients enrolled in that multicentre trial have produced interesting findings. Regional anaesthesia compared with general anaesthesia resulted in a greater percentage decrease in postoperative compared with preoperative concentrations of the pro-inflammatory cytokine IL-1β, an increase in the concentrations of anti-inflammatory IL-10, and a significant attenuation of MMPs involved in tumour migration and metastasis.\(^\text{[15]}\) Serum from the regional anaesthesia group reduced proliferation (but not migration) of an aggressive cancer cell line\(^\text{[105]}\) and increased apoptosis to a greater extent than serum from the general anaesthesia group.\(^\text{[105]}\) When incubated with serum from subjects receiving regional anaesthesia, donor NK cells demonstrated greater cytotoxicity than when exposed to serum from subjects in the general anaesthesia group.\(^\text{[106]}\)

Excised breast cancer specimens from the regional anaesthesia group demonstrated increased infiltration of NK and T-helper cells when compared with the general anaesthesia group.\(^\text{[107]}\) This same group of investigators also showed that paravertebral anaesthesia led to a significantly smaller increase than general anaesthesia in VEGF-C, which is known to promote angiogenesis and to be overexpressed in breast cancer.\(^\text{[107]}\) Another study, however, showed no difference between paravertebral block with sevoflurane general anaesthesia and general anaesthesia alone in terms of VEGF and PGE\(_2\) production, although the paravertebral group had lower glucose, cortisol, and C-reactive protein concentrations.\(^\text{[108]}\)

Both groups received diclofenac before surgery, which could have affected the results.

Prostate cancer

Prostate cancer is problematic in survival outcome studies because patients live for many years after diagnosis. It is estimated that cancer-specific survival in organ-confined prostate cancer is >95% at 10 yr.\(^\text{[109]}\) Patients with disease that has spread outside of the prostate are at increased risk of rapid progression. Reported cancer-specific survival rates and biochemical recurrence (BCR) at 10 and 15 yr are 63–90 and 25–79, and 40 and 60%, respectively.\(^\text{[109]}\) Therefore, when trying to discern a difference in survival between treatment groups it is most practical to enrol patients with advanced disease. Studies examining survival outcomes in prostate cancer often use BCR as an end point. Biochemical recurrence is often defined as either an increase of prostate-specific antigen from its postoperative nadir, or at a specific value such as >0.2 ng ml\(^{-1}\).\(^\text{[85]}\)\(^\text{[87]}\) Biochemical recurrence is an imperfect end point for studies because it does not translate into cancer-specific survival.\(^\text{[112]}\)

There have not been any randomized controlled trials examining the effect of regional anaesthesia on survival in prostate cancer. Most studies are retrospective. Two studies have shown an advantage of general combined with epidural anaesthesia and analgesia compared with general anaesthesia alone.\(^\text{[85]}\)\(^\text{[86]}\) Biki and colleagues\(^\text{[85]}\) examined 225 patients with invasive prostate cancer undergoing open radical prostatectomy, and patients receiving combined general and epidural anaesthesia and analgesia had a 57% (95% CI 17–78%) lower risk of BCR compared with those undergoing general anaesthesia with opioid analgesia. Wuethrich and colleagues\(^\text{[86]}\) examined 261 patients undergoing radical prostatectomy, ~50% of whom had invasive disease. They found that general and epidural anaesthesia and analgesia resulted in better clinical progression-free survival but found no differences between groups in terms of BCR-free survival, cancer-specific survival, or overall survival. One should be cautious in interpreting the lack of difference between groups, however, in light of the fact that the sample size was small, and as such, the study had sufficient power to detect only large differences. The general anaesthesia group also received ketorolac every 8 h, which might have confounded the results. Cyclooxygenase 2 is overexpressed in prostate cancer cells,\(^\text{[113]}\) and COX2 inhibitors have been shown to induce apoptosis in prostate cancer cells.\(^\text{[114]}\)\(^\text{[115]}\)

There are four studies in the literature showing no benefit for regional anaesthesia and analgesia in prostate cancer surgery.\(^\text{[87]}\)\(^\text{[88]}\)\(^\text{[89]}\)\(^\text{[90]}\) One retrospective study by Wuethrich and colleagues\(^\text{[89]}\) showed no difference in any end point, including BCR-free, local and distant recurrence-free, cancer-specific, and overall survival in patients with invasive prostate cancer undergoing radical prostatectomy with combined general and epidural anaesthesia and analgesia or general anaesthesia alone. This study was small, and the patients in the general anaesthesia group received ketorolac analgesia, which might have affected the results. The study by Forget and colleagues\(^\text{[88]}\) was large, with 1111 patients, and examined patients with localized disease undergoing radical prostatectomy. The goal of this study was to evaluate the impact of epidural anaesthesia and analgesia, along with a host of other analgesics, including sufentanil, ketorolac, clonidine, and ketamine, on BCR-free survival. The authors found a significantly reduced BCR-free survival rate associated with i.v. sufentanil, hazard ratio 7.78 (95% CI 5.79–9.78), but no significant effect from epidural analgesia or any of the other studied analgesics. Unfortunately, this study had a short follow-up time (mean 38 months), a significant number of patients receiving adjuvant treatments, and overlapping anaesthesia and analgesia regimens. Another study finding no difference in BCR in patients with localized disease was small and examined patients in a secondary analysis of a previous randomized controlled trial evaluating pain control, blood loss, and transfusion requirements.\(^\text{[89]}\) A large retrospective study by Roiss and colleagues\(^\text{[87]}\)
included 4772 patients undergoing radical prostatectomy with either general anaesthesia alone or general anaesthesia combined with single-injection spinal anaesthesia. They found no difference between groups in terms of overall survival, BCR-free survival, and overall survival. There were significant differences between groups with respect to prostate-specific antigen concentrations, tumour grade, and histology, although these differences were accounted for with propensity-score matching.

Colorectal cancer

Two studies evaluating the effect of regional anaesthesia on colorectal cancer recurrence after resection are secondary analyses of previously conducted randomized controlled trials that compared general and epidural anaesthesia and analgesia with general anaesthesia.92–93 The analysis by Myles and colleagues92 included a total of 446 patients, 230 of whom had epidurals. This study evaluated multiple types of abdominal cancer, including colorectal cancer. No difference in 5 yr mortality or recurrence rate was found between groups. The investigation was well powered to find a difference of one-third or greater, but any smaller differences might have been missed. Christopherson and colleagues93 found improved survival in patients with epidurals up to 1.5 yr after surgery. The group sizes were small, with 92 subjects in the general anaesthesia group and 85 in the epidural group, and 37% of patients had metastatic disease.

The other studies examining this question are retrospective.94–96 Cummings and colleagues97 examined 42,151 patients with colon cancer, 9670 of whom had epidurals, and found improved 5 yr survival in the epidural group (61 vs 55% in the general anaesthesia group). No difference in 4 yr disease recurrence was found between groups. Holler and colleagues95 included 749 patients and found an improved 5 yr survival in patients who received epidural anaesthesia compared with general anaesthesia (62 vs 54%, P<0.02). For ASA Class II–IV patients, there was significantly greater survival (P<0.009), but no difference between treatments for ASA Class I and II patients. Gupta and colleagues96 studied 655 patients, of whom 562 received epidurals and only 93 served as controls. They found a survival benefit for epidural anaesthesia and analgesia in rectal but not colon cancer. Gottschalk and colleagues96 found no overall difference in recurrence of colorectal cancer, but did find a lower risk of recurrence in the epidural group for those aged >64 yr. This study had a median follow-up time of only 1.8 yr. Finally, Day and colleagues97 observed no difference in overall survival or disease-free survival when comparing epidural, spinal, and patient-controlled analgesia in a total of 457 patients.

Other cancers

The association between regional anaesthesia and cancer recurrence has been studied retrospectively in other cancer types, including melanoma, cervical cancer, and laryngeal cancer. A single study has shown a benefit for regional anaesthesia and analgesia in 271 patients undergoing surgery for laryngeal and hypopharyngeal cancer.98 When compared with general anaesthesia alone, combined general and epidural anaesthesia with postoperative epidural analgesia resulted in significantly improved cancer-free survival and improved overall survival.

A protective role for regional anaesthesia has been seen in metastatic melanoma. Schlagenhauff and colleagues99 reviewed 4329 patients who received either general or local anaesthesia for melanoma excision. After adjusting for differences in tumour thickness and degree of invasion, general anaesthesia was associated with decreased survival. Another study, with a much lower number of patients (221 receiving general anaesthesia and 52 receiving spinal anaesthesia), found a non-significant trend towards longer cumulative survival in the patients undergoing spinal anaesthesia (96 vs 70 months, P=0.087).100 Two small, retrospective studies in cervical cancer have also suggested a benefit for regional anaesthesia. Lin and colleagues101 compared 106 patients receiving epidural anaesthesia and postoperative analgesia with 37 receiving general anaesthesia with postoperative opioid analgesia for ovarian cancer surgery. The 3 and 5 yr survival rates were 78 and 61% in the epidural group, and 58 and 49% in the general anaesthesia group. After adjustment for CA125 concentrations, histology, residual tumour, and lymphatic metastasis, general anaesthesia was associated with a hazard ratio of 1.214 (95% CI 1.075–1.431, P=0.043). De Oliveira and colleagues102 compared 127 patients receiving general anaesthesia alone with 26 patients with epidurals used both during and after surgery and with 29 patients with epidurals used only after surgery (both epidural groups also received general anaesthesia). The intraoperative and postoperative epidural group had a significantly increased time to recurrence and an increased mean time to death compared with both the general anaesthesia and the postoperative-only epidural groups (mean time to death 96 vs 71 and 70 months, respectively, P=0.01). Capmas and colleagues103 also found no benefit for a postoperative-only epidural infusion in 104 patients undergoing surgery for advanced-stage ovarian cancer.

Conclusions

During and after surgery, there are multiple factors at play in determining whether tumour cells released during primary tumour resection result in cancer metastasis and progression. Regional anaesthesia, analgesia, or both is unlikely to be the primary determinant in perioperative cancer progression, but one small part of the equation for certain cancers. Its use, however, may avoid exposure to other factors resulting in cancer progression, such as stress hormone release, uncontrolled or poorly controlled pain, and exposure to volatile anaesthetics and opioids. Multimodal perioperative pain regimens using regional anaesthesia in conjunction with other known protective measures, such as NSAIDs, may also be beneficial. Only well-conducted, large, randomized controlled trials, some of which are underway, will answer the question of whether regional anaesthesia can truly reduce cancer recurrence and increase survival.

Author’s contribution

T.T. conceived and wrote this review.

Declaration of interest

None declared.

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