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Centenary Review Article

CLINICAL PRACTICE

Tumour excisional surgery, anaesthetic-analgesic techniques, and oncologic outcomes: a narrative review

Orla Murphy[1], Patrice Forget[2,3,4], Daqing Ma[4,5] and Donal J. Buggy[1,4,6,*]

[1]Department of Anaesthesiology and Perioperative Medicine, Mater University Hospital, School of Medicine, University College Dublin, Dublin, Ireland, [2]Epidemiology Group, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, UK, [3]Department of Anaesthesia, NHS Grampian, Aberdeen, UK, [4]Euro-Periscope, The ESA-IC OncoAnaesthesiology Research Group, [5]Division of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK and [6]Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

*Corresponding author. E-mail: donal.buggy@ucd.ie

Summary

Cancer is a growing global burden; there were an estimated 18 million new cancer diagnoses worldwide in 2020. Excisional surgery remains one of the main treatments for solid organ tumours in cancer patients and is potentially curative. Cancer- and surgery-induced inflammatory processes can facilitate residual tumour cell survival, growth, and subsequent recurrence. However, it has been hypothesised that anaesthetic and analgesic techniques during surgery might influence the risk of cancer recurrence. This narrative review aims to provide an updated summary of recent observational studies and new randomised controlled clinical trials on whether certain specific anaesthetic and analgesic techniques or perioperative interventions during tumour resection surgery of curative intent materially affect long-term oncologic outcomes.

Keywords: general anaesthesia; intravenous anaesthesia; metastasis cancer; opioid cancer; postoperative analgesia; recurrence cancer; regional analgesia; surgery

Editor's key points

- Up to 70% of cancer is amenable to surgical resection, which offers the best chance of improved prognosis.
- It has been hypothesised that anaesthetic-analgesic technique influences oncologic outcome after excisional surgery.
- This review article provides an updated summary of recent observational studies and new randomised controlled clinical trials regarding the effect of anaesthetic and analgesic techniques on long-term oncologic outcomes.
- Further prospective research is required to investigate how perioperative interventions influence tumour-specific subtypes.

The question of whether anaesthetic-analgesic technique might influence oncologic outcomes after tumour excisional surgery is of enduring fascination >15 yr since it was initially hypothesised.[1] In 2020, 18 million new cancers were diagnosed worldwide, excluding non-melanoma skin cancer, and it is estimated that by 2040, the global cancer burden will increase to 28 million cases.[2] The primary tumour is rarely the cause of death for cancer patients. Rather, the metastatic process and resultant organ dysfunction are accountable for 80–90% cancer-related deaths.[3] Up to 70% of cancer is amenable to surgical resection, and it offers the best chance of improved prognosis.[4] This narrative review summarises the scientific rationale underpinning the hypothesis that the perioperative period could be inadvertently conducive to metastasis formation and future clinical recurrence and how standard anaesthetic and analgesic techniques during tumour resection

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surgery might favourably attenuate these processes. It will outline current laboratory, observational and where available, clinical trial evidence of the extent to which specific anaesthesia drugs and techniques potentially improve oncologic outcomes for patients, if at all (Table 1).

How the perioperative period could be conducive to cancer metastasis

Cancer comprises tumour cells surrounded by a specific tumour microenvironment. This microenvironment consists of an extracellular matrix, blood vessels, and various host cells (fibroblasts, mesenchymal, and various immune cells).[5] Moreover, a subset of tumour cells, 'cancer stem cells', which play an important role in facilitating tumour metastasis, are found within this environment. Cancer surgery can disrupt this environment and promote spread of invisible, microscopic residual cancer cells, which remain despite optimal surgical technique.[6]

Metastasis is a complex multistep process in which tumour cells disseminate from the primary neoplasm to secondary sites.[3,5] Postoperative cancer cell metastasis to distant organs and subsequent clinical recurrence may occur *via* local recurrence at the surgical resection site, lymph node metastasis, or secondary organ metastasis as a result of circulating tumour cells (CTCs) seeding before or during the perioperative period.[7] The likelihood for CTCs to survive and lodge in distant tissues during the perioperative period is not fully understood, but seems to be influenced by numerous immunomodulating factors[7,8] (Fig. 1). The pathophysiological mechanisms of metastasis may be described by the interaction between the surgical stress response, inflammation and perioperative immunologic modulation, pain, and angiogenesis (Fig. 1).

The surgical stress response and immunosuppression

The surgical stress response consists of two elements: the neuroendocrine-metabolic element and the cytokine-inflammatory-immune element.

The neuroendocrine-metabolic element is mediated by afferent somatic and autonomic nerves and elicits both a direct stress hormone and a sympathetic nervous system-mediated adrenergic response. It activates the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, causing the release of hormonal mediators, including catecholamines, prostaglandins, and growth factors.[9] These contribute to immunosuppression by impeding the anti-tumour activity of natural killer (NK) cells and CD8+ T cells and concurrently stimulating the proliferation of pro-tumour regulatory T cells and type 2 helper T cells.[10]

The cytokine-inflammatory element of the surgical stress response elicits transient immune impairment.[9] The immunologic response to cancer and surgery consists of adaptive and innate immune responses. Adaptive immune responses are slower onset, long duration, and specific to the antigen, and are mediated by antibodies and T cells. Innate immune responses are immediate and non-specific to the antigen and are mediated largely by neutrophils and NK cells.

Table 1 Summary of perioperative interventions and current available evidence: positive (+), neutral (0), negative (−) results or awaiting results of ongoing trial (?) with respect to tumour recurrence/survival rates. COX-2, cyclooxygenase-2; TIVA, total intravenous anaesthesia.

	In vitro (laboratory)	*In vivo* (animal)	Observational	RCT	Evidence
Regional anaesthesia			+/0	0	Neutral
Propofol TIVA/volatile anaesthesia	+/0	+	+/0	?	Vapor C awaited
Opioids	+/0	+/0	+/0	?	Further RCT needed
Amide local anaesthetic infusion	+	+	+/0	+/0/?	Encouraging early RCT data
NSAIDs/COX-2 inhibitors, beta blockers	+	+	+/0	0	Postoperatively alone – nil benefit, Pre/Intra/Post Combinations to be investigated
Dexamethasone	-		+/0	No data	RCT needed
Dexmedetomidine	-	-	0	+/0	Need adequately powered RCT
Ketamine	+/0	0	+	No data	RCT needed

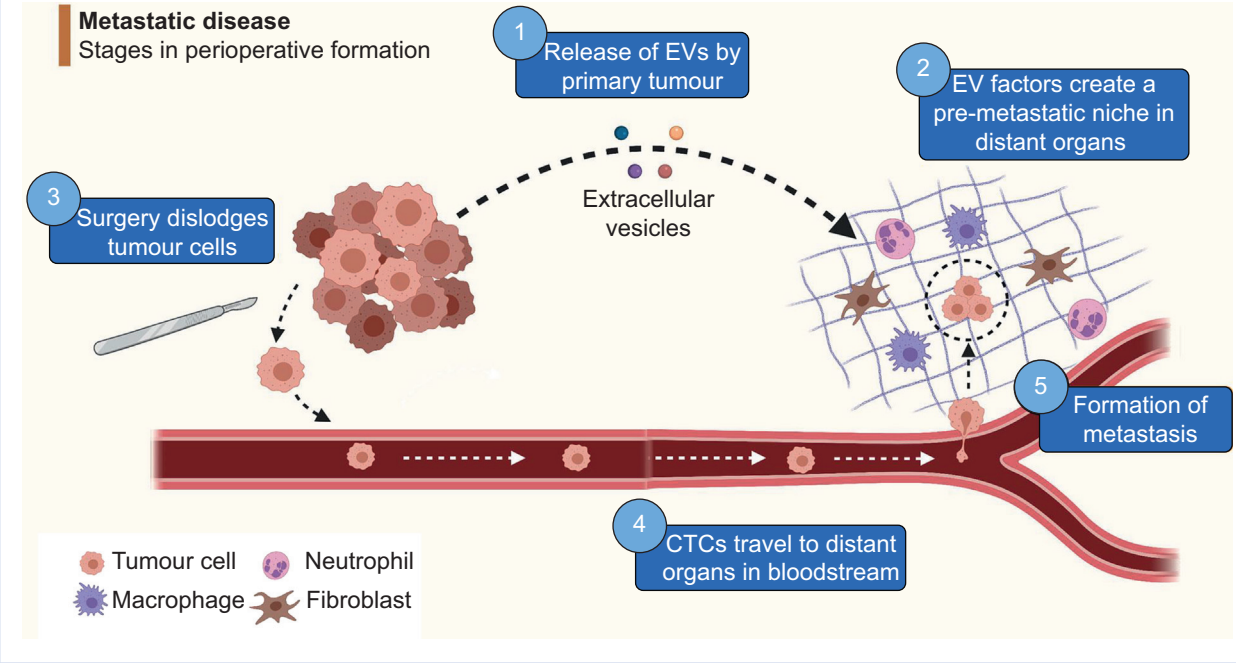

Fig 1. Schematic overview of pathophysiological mechanisms involved in perioperative metastasis formation. ① As it develops, the primary tumour releases extracellular vesicles (EVs) containing growth factors, miRNAs etc. ② EV-contained factors create a pre-metastatic niche in distant organs by stimulating local cells such as fibroblasts, macrophages, and mesenchymal stem cells to promote pro-neoplastic processes such as angiogenesis, inflammation, and stromal remodelling. ③ During surgery, malignant cells are dispersed from the primary tumour and are released into the bloodstream to form circulating tumour cells (CTCs). ④ CTCs are borne in the circulation to distant tissue beds where they arrest and extravasate into a pre-metastatic niche. ⑤ Survival conditions for the tumour cell are rendered even more favourable by the effects of mediators of the surgical stress response and inflammation, furthering the processes of angiogenesis, immune evasion etc. thus enabling the cancer cell to survive and proliferate and eventually form a clinically significant metastasis. (Created with BioRender®).

The innate and adaptive components of the immune system act in unison to eliminate cancerous cells.[10,11]

NK cells of the innate system, and T cells (helper CD4+ Th1 cells and cytotoxic CD8+ T cells) of the adaptive system provide cell-mediated immunity (CMI), which is the most important cellular anticancer immune response.[10] This activity is influenced by postoperative pathophysiological changes—the initial inflammatory state is followed by a period of transient immunosuppression during which CMI is diminished.[11]

When the surgical stress response activates its neuroendocrine-metabolic element, cortisol and catecholamines are released which inhibit the antitumour activity of NK cells and CD8+ T cells. NK cytotoxicity is also reduced by increases in interleukin-6 (IL-6) and prostaglandin E2.[12] CMI is influenced by helper T lymphocytes, which can be classified as Th1 cells favouring a cancer resisting CMI effect, and Th2 cells favouring antibody-mediated immunity. Postoperatively, Th2 proliferation increases, shifting the Th1/Th2 balance from a Th1-predominant CMI phenotype towards Th2 dominance, so the routine pathophysiological response to surgery could inadvertently protect cancer cells from immune attack.[13]

The identification and eradication of cancer cells are crucial components of human immunity, and fundamental to this is the activity of the NK cells of the innate immune system and the cytotoxic CD8+ T cells of the adaptive immune system.[14] Prostaglandins and catecholamines can activate receptors such as β2-adrenergic and prostaglandin receptors that might have direct pro-tumour effects.[15,16]

Perioperative neutrophils in metastasis

Once considered relatively passive, recent investigation points to neutrophils having an important role in carcinogenesis.[17] Circulating neutrophil counts are often increased by the postoperative inflammatory state, leading to an increased neutrophil-to-lymphocyte (NLR) ratio. NLR elevation is associated with poorer survival in some cancers. It is modulated by anaesthetic technique—but whether this reflects causation or merely correlation is unclear.[18] Circulating neutrophils can migrate into the tumour microenvironment where they adopt an anti- or pro-tumour phenotype, termed N1 and N2, respectively. N1 neutrophils phagocytose cancer cells whereas N2 neutrophils promote cancer in numerous ways, including by reshaping peritumour stroma or by expressing vascular endothelial growth factor (VEGF) or *matrix metalloproteinase*-9 (MMP-9).[19] Neutrophils can also extrude decondensed chromatin to form web-like structures called neutrophil extracellular traps (NETs). This process (termed NETosis) is implicated in neoplasia with elevated serum markers of NETosis associated

with poorer prognosis in certain cancers.[20,21] There are some data that perioperative lidocaine may modulate NETosis, but whether that translates into oncologic improvement remains to be seen.[21]

Inflammation

Tissue injury creates an inflammatory state necessary to recruit and activate the cellular components responsible for wound healing. Macrophages and dendritic cells are activated and produce chemokines and pro-inflammatory cytokines including interleukins (such as IL-1, IL-1β, IL-6, IL-8, IL-12), tumour necrosis factor alpha (TNF-α), and prostaglandins.[22] Rapid increases in inflammatory mediators not only promotes local tissue healing, but also stimulates cancer cell survival and proliferation.[23] The immune system and the sensory nervous system (SNS) are closely integrated: pro-inflammatory cytokines modulate pain transmission, causing peripheral and central pain sensitisation, increasing SNS and HPA axis outflow, in turn stimulating cytokine expression by immune cells. Expression of numerous signalling pathways are altered in the post-surgical inflammatory milieu, many of which are associated with cancer progression, including enzymes such as COX-2, matrix metalloproteinases (MMPs), and transcription factors such as nuclear factor kappa-beta (NF-κB).[24] Inflammatory cytokines impair endothelial integrity and endothelial function has been demonstrated to deteriorate for several days after surgery. Loss of endothelial function enables leucocyte transmigration and potentially facilitates the extravasation of CTCs into remote tissues.[25] The tyrosine kinase Src kinase contributes to this process *via* its action as a regulator of endothelial barrier integrity. Src kinase is activated by inflammatory mediators, including TNF-α, resulting in disruption of tight junctions between endothelial cells and eventual loss of endothelial function.[26]

Angiogenesis

Angiogenesis is the creation of new blood vessels by tumour tissue for tumour tissue, parasite-like, in response to the hypoxic cellular microenvironment tumour tissue itself. Surgical tissue injury causes localised tissue hypoxia, resulting in upregulation of hypoxia-inducible factor (HIF), in turn stimulating expression of VEGF. VEGF drives the synthesis of numerous tissue components involved in angiogenesis including integrins and extracellular matrix.[27,28] Similarly, rapid growth of cancerous tissue creates a hypoxic cellular microenvironment, stimulating HIF and VEGF expression to create new blood vessels to supply the oxygen and nutrients necessary for further neoplastic expansion. Overexpression of HIF and VEGF is associated with poorer prognosis in certain cancer types, including pancreatic and ovarian cancer.[28] Overall, it is clear that a number of pathophysiologic processes during the perioperative period could create conditions conducive to tumour cell survival.

How routine anaesthesia and analgesia interventions might modify perioperative factors and potentially promote metastasis

A schematic diagram showing how different anaesthetic or analgesic drugs might affect cancer cell biology is presented in Figure 1. Regional anaesthesia attenuates the surgical stress response. Attenuation of the stress response may reduce the immunosuppression associated with the perioperative period, minimise the use of volatile anaesthesia and opioid requirement as a result of improved pain control, and therefore preserve the immune system's capacity to eliminate residual cancer cells.[29]

Regional anaesthesia has the potential to reduce, as analgesia, or replace, as anaesthesia, volatile anaesthetics intraoperatively. Volatile anaesthesia has been shown to have effects on the immune system and the inflammatory response that may directly affect cancer cell survival.[30] These effects include modulating cellular targets on immune cells (such as neutrophils, macrophages, and NK cells) and upregulating anti-apoptotic pathway signalling.[31] However, the molecular mechanisms for these effects are incompletely understood, and there is conflicting evidence among the inhaled agents and among different cancer cell lines. For example, in a laboratory study, sevoflurane exposure stimulated renal cancer cells, but had an inhibitory effect on non-small-cell lung carcinoma (NSCLC).[32]

Uncontrolled pain has also been shown in animal studies to suppress NK cells and promote metastasis; therefore it has been hypothesised that by minimising postoperative pain, regional anaesthesia could have a beneficial effect on the immune system.[33] A systematic review and meta-analysis of experimental animal data compared the risk of cancer metastasis between cohorts that received excellent analgesia compared with standard analgesia. Analgesics, in particular NSAIDs, significantly reduced the risk of metastasis in various animal models.[33]

Reduced pain allows for opioid dose reduction. Opioid analgesics are reported to inhibit cellular and humoral immune function and increase angiogenesis. Direct effects on immune function may occur via opioid receptors, such as the μ-opioid receptor (MOR), or non-opioid receptors expressed by immune cells, including NK cells.[34] However, recent data suggest the effect of opioids during cancer surgery may be more nuanced, depending on the specific subtype of tumour and patient-specific expression of genes by the tumour itself.[35]

Plausible experimental evidence suggests that amide local anaesthetics possess direct immune-preserving and anti-inflammatory qualities.[36] They also inhibit cancer cell biology *in vitro* in some tumours, by a combination of sodium channel inhibition, inhibition of the Src oncogene, and DNA demethylation.[37,38] *In vivo* evidence supports a beneficial effect of intravenous lidocaine in metastatic burden in mouse models of cancer[39] (Fig. 2). Available clinical evidence for its potential effect is presented below.

Propofol provides suppression of prostaglandin and cytokine production, prevents immunosuppression, reduces migration of cancer cells through MMP suppression, and provides increased activity of NK cells. Furthermore, propofol has been shown to reduce both cancer cell motility and the degree of invasiveness, and lastly gives reduction of HIF-1-alpha.[40,41]

Both catecholamines and prostaglandins have been implicated in the progression of metastasis. A pro-inflammatory state is created by a combination of factors, including surgical stress response, patient pain and anxiety, and from the tumour tissue itself. While the release of inflammatory mediators is required for physiological wound healing to occur, it could theoretically also promote the viability of any residual cancer cells by both immunosuppression and stimulation of cell proliferation.[41,42] However, NSAIDs, used during surgery for their analgesic effects, may also play a role via the

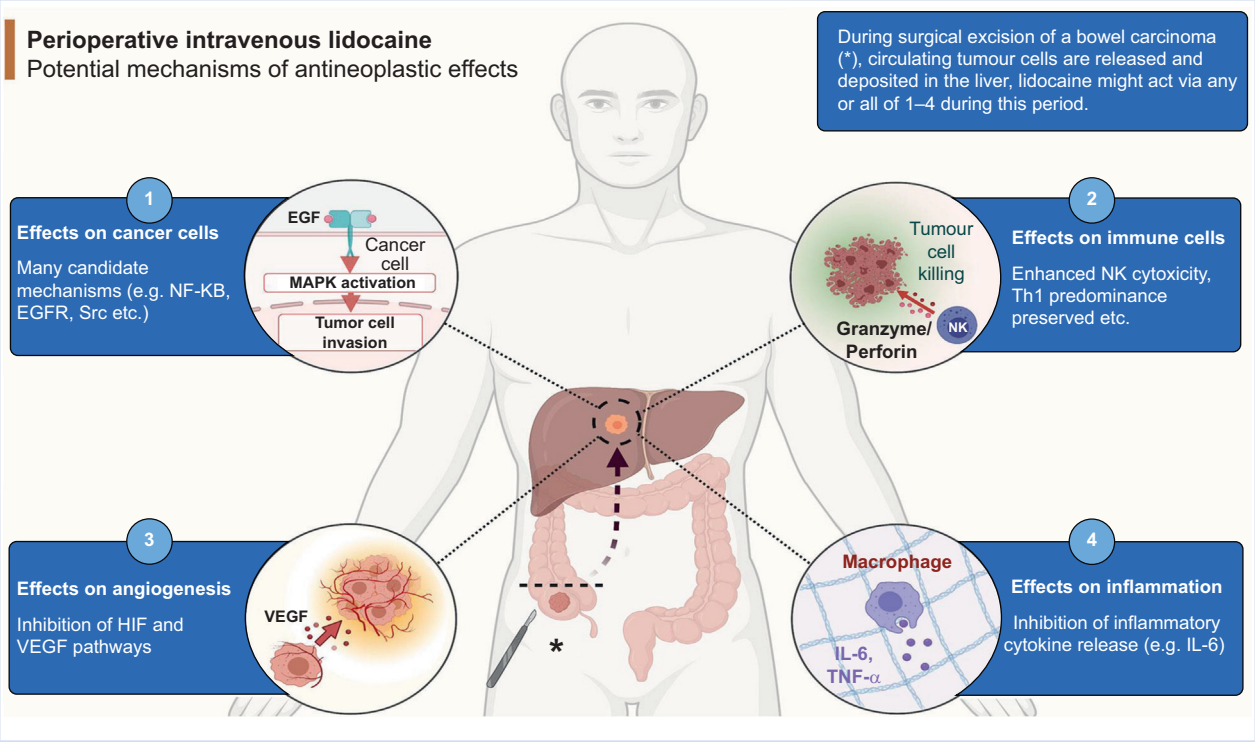

Fig 2. Potential anti-neoplastic mechanisms of action of systemic lidocaine during in colorectal (and other) cancers surgery. As a colonic (or other) tumour is excised (marked with *), tumour cells are released into the circulation to form circulating tumour cells (CTCs). These CTCs arrest within liver parenchyma where the likelihood of forming future clinically significant metastatic disease depends on the balance of pro- and anti-neoplastic processes present in the tumour microenvironment. Perioperative systemic lidocaine bathes the tumour cells and their microenvironment during this sensitive period and potentially beneficially alters the odds of host survival via an effect on any of ① to ④ outlined in the figure. (Created with BioRender®). EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HIF, hypoxia-inducible factor; IL-6, interleukin-6; MAPK, mitogen-activated protein kinase; NK, natural killer; NF-κB, nuclear factor kappa-beta; TNF-α, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.

inhibition of prostaglandin synthesis and immune function and therefore limit inflammation-induced tumour growth.[42,43]

While these laboratory-based studies suggest a scientific rationale, whether any single drug or technique, or any combination might deliver altered oncologic outcome in patients after cancer resection surgery, can only be proved by clinical studies. We now present a technique-by-technique summary of available evidence.

Acute pain control

Theoretically, good acute perioperative pain control is challenging in patients after cancer surgery for many reasons, including prior opioid analgesia and therefore postoperative opioid tolerance; additional anxiety related to their diagnosis of cancer, exacerbating acute pain; and often more extensive surgery, with an associated extensive stress response. These factors could potentially aggravate tumour cell microenvironment conditions which may be conducive to tumour cell survival and metastasis. Poorly controlled postoperative pain is itself associated with postoperative complications. For all these reasons, optimising postoperative acute pain management is an important goal for the anaesthesiologist.[44] This may be achieved by any combination of techniques, and associated with obtunding of the surgical stress response, and could theoretically reduce cancer recurrence risk. It would undoubtedly be unethical to test this hypothesis in a prospective, RCT in patients undergoing cancer surgery. Instead, observational retrospective data of 2401 patients who underwent colorectal cancer resection included 13 931 pain score observations. Approximately 10% of these surgical patients had persistent moderate to severe pain up to 5 days postoperatively and this cohort had the highest risk of cancer recurrence and mortality when compared with patients who experienced mild postoperative pain.[45]

Regional anaesthesia

The first anaesthetic technique to be evaluated for its potential effect during cancer resection surgery on long-term oncologic outcomes was regional anaesthesia, specifically paravertebral anaesthesia during breast cancer resection.[1] The rationale was that surgical stress response-induced inflammation and postoperative pain could support residual cancer cell survival and inhibit immune function. Attenuating this with regional anaesthesia might prevent this and reduce risk of tumour recurrence and metastasis. Other observational studies soon followed, evaluating the role of various regional techniques, especially epidural anaesthesia on long-term oncologic outcomes, which yielded conflicting results. The first prospective

follow-up investigation was among patients who were originally randomised to receive epidural anaesthesia or not for major noncardiac surgery, with mortality and major morbidity being the endpoints. Long-term follow-up data were available for 94% (n=446) of eligible participants. The median time to recurrence of cancer or death was 2.8 yr (95% confidence interval [CI] 0.7–8.7 yr) in the control group and 2.6 yr (0.7–8.7 yr) in the epidural group (P=0.61). Recurrence-free survival was similar in both epidural and control groups (hazard ratio [HR] 0.95, 95% CI 0.76–1.17; P=0.61), indicating no causal effect of epidural anaesthesia on oncologic outcome.[46]

A large Danish registry-based, propensity score-matched, retrospective study among almost 6000 colorectal cancer patients evaluated patients who had either general anaesthesia (GA) and epidural anaesthesia combined for tumour resection surgery or GA alone. The median follow-up time was 58 months (inter-quartile range [IQR] 29–86 months). No significant difference was observed in terms of recurrence (HR 0.91, 95% CI 0.82–1.02) or mortality (HR 1.01, 95% CI 0.92–1.10).[47] Despite the large size and optimal management of this and other large retrospective analyses, such studies can never prove a causal effect of any anaesthetic technique on cancer outcome. This requires prospective, randomised controlled clinical trial evidence. The original and largest multicentre RCT (n=2108) compared patients undergoing potentially curative primary breast cancer resections to either regional anaesthesia-analgesia (paravertebral blocks and propofol total i.v. anaesthesia—TIVA) or GA with sevoflurane maintenance and opioid analgesia. Median follow-up time was 36 months (IQR 24–49 months), and the study was stopped after a pre-planned futility boundary was reached. Cancer recurrence was 10% in both groups (HR 0.97, 95% CI 0.74–1.28; P=0.84) indicating that the choice of regional or volatile anaesthetic technique has a neutral effect on breast cancer recurrence rates.[48] A small RCT among n=180 patients who were randomised to receive either epidural anaesthesia or systemic opioid analgesia after primary colorectal cancer surgery found no difference in oncologic outcomes after 2 yr. However, this study was clearly underpowered to evaluate long-term cancer outcomes.[49]

A new Chinese prospective RCT designed to evaluate two endpoints has been evaluated in terms of cancer patients' oncologic outcomes. Comprising >1700 older patients (60–80 yr) and designed to evaluate both postoperative delirium up to 7 days after major noncardiac surgery, and long-term oncologic outcome, it randomised patients to receive combined epidural and GA *vs* GA only. Whereas patients in the epidural arm of this trial had reduced delirium, there was no difference between the techniques in overall survival (HR 1.07, 95% CI 0.92–1.42, P=0.408) or cancer-specific survival (HR 1.09, 95% CI 0.93–1.28, P=0.29).[50] A smaller trial, with oncologic outcome as its primary endpoint, hypothesised that combining epidural anaesthesia-analgesia with GA would improve recurrence-free survival as the primary endpoint after lung cancer surgery. This RCT (n=400) of patients undergoing video-assisted thoracic surgery (VATS) for lung cancer, randomised patients to GA with i.v. opioid analgesia or GA and epidural anaesthesia combined. The median follow-up was 32 months (IQR 24–48 months). No difference was observed in overall survival (adjusted HR 1.12, 95% CI 0.64–1.96, P=0.7) or recurrence rates (adjusted HR 0.9, 95% CI 0.6–1.35, P=0.6) between the two groups.[51]

Therefore, the question of whether regional anaesthesia during cancer resection influences long-term oncologic outcome has been definitively addressed, and the answer is emphatically that it is neutral.

Propofol total intravenous anaesthesia *vs* volatile agent anaesthesia

Building on laboratory work suggesting a potential benefit of propofol TIVA over inhalation anaesthesia because of its anti-inflammatory and immune neutral effects, a meta-analysis of 23 retrospective observational studies (n=1611) nonetheless found no difference in perioperative blood inflammatory marker levels IL-6, IL-10, TNF-α, and C-reactive protein (CRP) between the two techniques.[52]

Retrospective observational studies have suggested that the use of propofol TIVA may be advantageous in comparison with inhalation volatile agents for cancer patients undergoing primary resection, in terms of recurrence and overall survival. Such an analysis of >3000 patients receiving surgery for a wide variety of tumours under either non-randomised propofol TIVA or inhalation sevoflurane in >1500 propensity-matched pairs, found an association between propofol anaesthesia and slightly better oncologic outcomes.[53] A meta-analysis of heterogeneous retrospective studies, amounting to >23 000 patients across a wide range of tumours comparing propofol based TIVA with volatile-based anaesthesia during primary cancer resection surgery, found an association between propofol and better overall survival (HR 0.79, CI 0.66–0.94), but no difference in recurrence-free survival (HR 0.81, CI 0.61–1.07).[54]

The largest observational studies are from Scandinavian national databases. A propensity score-matched cohort of >4600 matched pairs of breast cancer patients receiving maintenance anaesthesia of either propofol TIVA or volatile agent for breast cancer surgery found no difference in overall survival between the two groups at median 1 yr follow-up.[55] However, a similarly sized, propensity-matched Danish registry study of colorectal cancer patients found an association between inhalation anaesthesia during tumour resection and increased risk of recurrence (HR 1.12, 95% CI 1.02–1.23).[56] Another large Japanese register-based retrospective cohort study (n>190 000) reviewed patients receiving either volatile or TIVA anaesthesia from July 2010 to March 2018. Results were similar, neither overall survival (HR 1.02, 95% CI 0.98–1.07) nor recurrence-free survival (HR 0.99, 95% CI 0.96–1.03) being associated with any apparent advantage in terms of cancer outcomes.[57]

As with many questions in this field of onco-anaesthesiology, further RCTs are awaited to provide further information, but the current signals are indicating a neutral effect of propofol TIVA on long-term oncologic outcomes. A double-blind RCT assigned primary breast cancer patients (n=210) to either sevoflurane or propofol TIVA maintenance anaesthesia, with the primary outcome being CTC counts, which were measured postoperatively at three distinct time points (0 h, 48 h, and 72 h). No difference in CTC counts were observed.[58] In a pilot, prospective, randomised, single-blind trial, serum from patients (n=40) enrolled in the Breast

Cancer Recurrence and Anaesthesia trial was examined for markers of NETosis (a cellular phenomenon implicated in cancer progression and metastasis) just before and at 24 h after surgery. No difference was found in these markers between patients receiving volatile opioid or regional and propofol TIVA-based techniques.[59]

A modestly sized RCT (n=153) among colorectal cancer patients, randomised patients to receive either propofol TIVA or sevoflurane anaesthesia in South Korea.[60] The primary outcome was the fraction of circulating NK immune cells (NK cells) and T cells in the two groups. These cells have a particular role in resisting CTCs and preventing metastasis development. There was no significant difference in circulating NK or T cells postoperatively.

Another possible biomarker of metastasis in perioperative care is NLR. Inflammation and immunosuppression contribute to the pathogenesis of cancer. An increased NLR reflects these processes and is associated with adverse cancer outcomes. A secondary analysis was preformed of a RCT of breast cancer patients who underwent tumour resection. These patients were randomised to receive either paravertebral regional anaesthesia with propofol TIVA or general anaesthesia with a volatile agent with opioid analgesia. Postoperative NLR was lower (3.0 [2.4–4.2] *vs* 4.0 [2.9–5.4], P=0.001) in the propofol-paravertebral group, suggesting that propofol-paravertebral anaesthesia attenuated the postoperative increase in the NLR.[18] However, this did not translate into long-term oncologic benefit in the subsequent breast cancer recurrence trial, as outlined above.[51]

An RCT[61] comparing propofol *vs* volatile agent among 1700 Chinese patients having major cancer surgery, which also evaluated neurocognitive outcomes, was published recently. Just under 1200 older Chinese patients (65–90 yr), undergoing surgical resection of a wide variety of tumours, were randomised to receive either sevoflurane volatile anaesthesia or propofol TIVA. At the end of follow-up (median 43 months), there were 188 deaths amongst 598 patients (31%) assigned to propofol-based anaesthesia compared with 175 deaths amongst 597 patients (29%) assigned to sevoflurane-based anaesthesia; adjusted HR 1.02; 95% CI 0.83–1.26; P=0.834. Recurrence-free survival was 223/598 (37%) in patients given propofol anaesthesia *vs* 206/597 (35%) given sevoflurane anaesthesia; adjusted HR 1.07; 95% CI 0.89–1.30; P=0.465. The authors concluded that propofol TIVA should not be promoted to cancer patients in any expectation that it would affect cancer recurrence.

Taken together, although there is a signal from some large retrospective registry-based studies that propofol may be associated with prolonged disease-free survival and even overall survival after surgical resection in some tumours, compared with volatile agent, available modestly-sized RCTs do not support this hypothesis. This question, and whether lidocaine can influence the oncologic outcome, should be definitively addressed by the recently commenced VAPOR-C trial.[62] VAPOR-C has oncologic outcomes as its primary raison d'être and is randomising patients with colorectal cancer and NSCLC, avoiding the heterogeneity of tumours included in the Chinese follow-up analysis.

Opioids

Various laboratory studies have indicated that opioids have both indirect and direct effects on the immune system which may promote tumour evasion or survival. Opioid agonism at various sites in the nervous system inhibits release of biological amines, which attenuates innate immunity.64 MORs are expressed both by immune cells and some tumour cells. In terms of opioids' effects on immune cells, laboratory data have indicated that some opioids suppress NK cells whereas others prevented this.[63,64] MOR expression and signalling may lead to cancer progression via angiogenesis and other cellular pathways, and some studies found an association between higher MOR expression and higher risk of cancer metastasis.[64] This led to concern that perioperative opioid analgesia could inadvertently stimulate cancer progression or recurrence.

An analysis of large public gene repositories of solid tumours suggested that whereas the expression of specific opioid receptors varied within tumours, there was no association between tumour opioid receptor expression and prognostic outcomes.[65]

A retrospective analysis of human hepatocellular carcinoma suggested an association between higher tumour MOR expression and more aggressive disease and worse prognosis. *In vitro* studies of these tumour cell lines supported this, in which the overexpression of MOR promoted cell growth and metastasis. Consistent with these observations, *in vitro* studies demonstrated suppressed cancer cell growth and metastasis with MOR inhibitors.[66]

In medical oncology research, two fundamental principles are firstly, that cancer is not a single disease, but rather different tumour types may respond differently to any given therapy and secondly, a key predictor of the link between a treatment and outcome is individual patient-specific tumour genomic differences.[35] A retrospective study assessed the differential expression of opioid receptors between healthy and tumour tissue in patients with Stage 2 and 3 colon cancer undergoing elective surgery. The primary endpoint was the difference in MOR expression between tumour tissue and healthy tissue in subjects with or without recurrence. Whereas there was a significant difference in MOR and opioid growth factor receptor (OGFR) expression between tumour tissue and control tissue in those patients with Stage 2 or 3 colorectal cancer, this was not associated with recurrence.[67]

A retrospective analysis of 740 patients and their excised lung adenocarcinoma tumours (Stage 1–3) questioned if intraoperative opioid use was associated with oncologic outcomes in early-stage disease. Higher intraoperative oral morphine equivalents were associated with worse overall survival if the patients' tumour expressed higher *CKDN2A* gene alterations. In contrast, alterations in other oncogenic pathways were associated with improved recurrence-specific survival at higher morphine doses, suggesting that intraoperative opioid dose is associated with different cancer outcomes depending on the different expression of individuals' tumour genes.[68]

A retrospective analysis of 1143 triple-negative breast cancer tumours for pro-tumour and antitumour receptors found that, in multivariable analysis, higher intraoperative opioid dose was associated with favourable recurrence-free survival, HR 0.93 (95% CI 0.88–0.99) per 10 oral morphine milligram equivalents increase (P=0.028), but was not significantly associated with overall survival, HR 0.96 (95% CI 0.89–1.02) per 10 morphine milligram equivalents increase (P=0.2). By analysis of publicly available genetic sequences of these triple-negative tumours, an upregulation of opioid receptors within the tumour was associated with a protective effect on cancer recurrence, whereas the pro-tumour TLR-4 was downregulated, supporting the idea that patient-specific

tumour gene expression may be an important determinant of oncologic outcome.[69]

In contrast, a retrospective population-based cohort study of cancer outcomes in patients with chronic pain who were chronic opioid users (prescribed >180 defined daily doses of analgesics/year), was compared with chronic pain patients who were low opioid users before they received a cancer diagnosis. The analysis showed that the HR for the primary endpoint of overall survival in patients receiving long-term opioids was 3.5 (95% CI 3.0–4.1, P=0.001). The adjusted HR for overall survival in patients receiving long-term opioids was 3.53 (95% CI 3.03–4.11; P<0.001), suggesting that long-term opioid analgesic use before cancer diagnosis might be associated with poorer overall survival in patients with chronic pain compared with such patients who did not receive long-term opioid analgesics.[70]

A retrospective cohort study (n=366) examined MOR expression in patients undergoing primary debulking surgery for ovarian cancer. Whereas no difference in overall survival or disease-free survival was observed, patients with tumours expressing high levels of MOR had higher intraoperative opioid consumption levels, and higher perineural nerve invasion rates.[71]

Bringing these laboratory data to the clinical environment, a small, underpowered Brazilian RCT randomised n=146 prostatectomy patients to either opioid-free or opioid-based anaesthesia, to test the hypothesis that opioid-free anaesthesia might cause less biochemical recurrence, measured by increases in prostate-specific antigen. There was no difference in terms of biochemical recurrence between the two groups: 17 biochemical recurrences in the opioid-free group *vs* 14 in the opioid-based group (P=0.54). This suggests that opioids do not affect oncologic outcomes in this context, consistent with the findings of a recent meta-analysis of retrospective data comparing opioid-free with opioid-based anaesthesia in cancer surgery.[72] However, while RCTs are the way to go to address this question, this one was grossly underpowered to address the question.

In summary, the effect of perioperative opioids on oncologic outcomes is nuanced. Laboratory models suggest that they might inhibit immune function and facilitate cancer cell biologic function, thereby potentially supporting cancer cell dissemination. This experimental model signal is more than offset by multiple observational clinical studies involving excised patients' tumour tissue, which indicate an association between increased opioid use and improved oncologic outcome in certain tumour subtypes and if certain opioid genes are expressed within patient-specific tumours.

Future prospective trials should strive to evaluate the effect of perioperative interventions on cancer subtypes and if feasible, to also evaluate relevant patient-specific genomic expression within the excised tumour.

Amide local anaesthetics

Whereas laboratory data suggest a plausible scientific rationale for a beneficial effect of amide local anaesthetics in cancer cell biology,[36,38] clinical observational studies have generated a mixed signal, but RCTs are just beginning to emerge. Lidocaine is the prototype amide local anaesthetic. Unlike other members of this family, lidocaine may be given safely systemically, provided it is administered with caution and appropriate monitoring. Despite the well-described safety profile in numerous clinical trials, systemic lidocaine has a very narrow therapeutic index; central nervous system (CNS) toxicity occurs (>5 μg ml^{-1}) slightly above the therapeutic plasma concentration (2.5–3.5 μg ml^{-1}). The factors that influence the plasma concentration of free lidocaine include the dose and rate of injection, acid–base status, hypercapnia and hypoxia, low plasma protein concentrations, and diminished hepatic or renal function. When the plasma concentration of lidocaine exceeds 5 μg ml^{-1}, patients will first exhibit CNS symptoms of toxicity.[73] Multiple trials and clinical experience have demonstrated its safety when i.v. lidocaine is administered as a bolus 1.5 mg kg^{-1} followed by a continuous infusion at 1.5–2.0 mg kg^{-1} h^{-1}; it results in plasma concentrations that remain below 5 μg ml^{-1}. Lidocaine at this plasma concentration is adequate to attenuate sympathetic responses, decrease pain, and demonstrate a significant volatile anaesthetic and opioid-sparing effect. This use of lidocaine for up to 24 h has been widely reported to show a significant decrease in pain, reduce analgesic requirements along with a faster return of intestinal function, and overall reduction in side-effects.[73,74] A retrospective study among 2239 patients undergoing pancreatic resection for cancer found that patients given systemic lidocaine administration (bolus i.v. lidocaine 1.5 mg kg^{-1} at induction, followed by infusion 2 mg kg^{-1} h^{-1}), decreased intraoperative opioid and postoperative rescue analgesia compared with patients not receiving lidocaine. There was better overall survival with lidocaine at 3 yr (HR 0.62, 95% CI 0.29–0.78), but not disease-free survival.[75] However, as is often the case in clinical research, this signal from their observational study was not substantiated in a subsequent prospective RCT, where the same group randomised n=563 pancreatic cancer resection patients to i.v. lidocaine or placebo perioperatively. Overall survival (HR 0.98, 95% CI 0.8–1.2) and disease-free survival (HR 0.9; 95% CI 0.7–1.2) were not influenced by lidocaine.[76]

Neutrophil Extracellular Trapping (NETosis) is an immune function whereby external antigens or pathogens, including tumour cells, are engulfed by neutrophils, which then extrude their contents into the blood leaving a residual marker which may be detected by serology. NETosis is thought to be a marker of metastases in breast and other tumours.[20] In a small RCT (n=120), patients undergoing breast cancer excision were randomised to receive i.v. lidocaine as bolus 1.5 mg kg^{-1} followed by infusion 2 mg kg^{-1} h^{-1} during surgery or placebo perioperatively. Patients were simultaneously randomised to receive propofol TIVA or sevoflurane GA in a 2×2 factorial design trial. I.V. lidocaine attenuated the surgical stress response-induced inflammatory markers and serum NETosis expression in comparison to placebo.[21] Similarly, 60 patients undergoing early-stage NSCLC excision via VATS were randomised to receive perioperative lidocaine infusion or placebo. There were lower IL-17 and serum cortisol concentrations at 24 h postoperatively in the lidocaine group (P=0.038) on discharge from PACU, suggesting attenuation of the surgical stress response and a potentially beneficial effect on oncologic outcomes.[77]

Encouragingly, a small RCT (n=40) randomised women after laparoscopic resection of ovarian cancer to receive intraperitoneal infiltration and infusion of amide local anaesthetic ropivacaine *vs* intraperitoneal saline for postoperative analgesia. Intraperitoneal ropivacaine decreased the time to return to intended oncologic therapy (RIOT).[78] RIOT is a new surrogate outcome measure which reflects how well patients

having primary tumour resection recover from surgery. It may be an indicator of subsequent oncologic outcome, although this remains to be proved.[79]

Further, a large-scale RCT from a number of Indian centres among women undergoing breast cancer surgery of curative intent has just been reported. This group randomised almost 1600 women to an active arm (who received infiltration of amide local anaesthetic lidocaine 0.5 mg kg^{-1} up to 4.5 mg kg^{-1} body weight, 7–10 min before surgical excision 'LA'), compared with a control group, who did not receive this lidocaine infiltration ('no LA'). Median follow-up time was >5.5 yr (68 months). In the LA and no LA arms, 5-yr disease-free survival rates were 87% and 83% (HR 0.74; 95% CI 0.58–0.95; P=0.017) and 5-yr overall survival rates were 90% and 86%, respectively (HR 0.71; 95% CI 0.53–0.94; P=0.019). The impact of LA was similar in subgroups defined by menopausal status, tumour size, nodal metastases, and hormone receptor and human epidermal growth factor receptor 2 status. No adverse effects from lidocaine were observed.[80] This is the first trial to report a positive difference of a single perioperative intervention on long-term oncologic outcomes and will encourage ongoing efforts among anaesthesiologists and other clinicians to complete other ongoing trials, testing the long-term oncologic effects of various perioperative interventions during primary cancer surgery, in the field of onco-anaesthesiology.

Overall, therefore, whereas there are laboratory mechanisms of action of amide local anaesthetics which indicate that these agents inhibit cancer cell biological functions, observational and small RCTs do not support the hypothesis that systemic lidocaine might affect long-term oncologic outcomes. However, the positive findings of the recent trial from India demonstrating a benefit of large volumes of locally infiltrated lidocaine before breast surgery in improving disease-free survival, is in contrast to the smaller trials on systemic intravenous lidocaine. The ongoing VAPOR-C trial is a 2×2 factorial design trial randomising patients to receive either propofol i.v. or volatile anaesthesia during primary colorectal carcinoma or NSCLC excision. Within these trial arms, patients will also be randomised to receive systemic lidocaine or not. This trial will be adequately powered to detect clinically meaningful differences in disease-free survival after 5 yr.[62]

NSAIDs/COX-2 inhibitors and beta blockers

Despite the positive effect of NSAIDs in laboratory studies, there is insufficient or inconclusive evidence from high-quality clinical studies to support the experimental data, which suggests that these agents would attenuate cancer cell survival and metastasis.[81,82] Beta-adrenergic signals mediate much of the surgical stress response via the sympathetic nervous system. Therefore, it is hypothesised that blocking this signalling pathway might have beneficial effects on risk of tumour recurrence.

New RCTs have evaluated the hypothesis that beta blockers and NSAIDs combined might influence cancer recurrence after tumour resection surgery of curative intent. A small trial (n=34) randomised colorectal cancer patients to either propranolol and etodolac (COX-2 inhibitor) or placebo for 20 days starting 5 days pre-surgery. There were beneficial effects on some biomarkers of metastasis, and actual recurrence rates were 2/16 in the treatment cohort *vs* 6/18 in the placebo cohort).[83] In a placebo controlled RCT, a single dose of 30 mg ketorolac in a trial (n=203), given before the surgical incision in high-risk breast cancer patients, did not significantly modify disease-free survival. However, no NSAIDs were used after surgery in this study.[84]

Two larger trials have shown no benefit of NSAIDs in terms of disease-free survival. The REACT trial randomised breast cancer patients after surgical resection (n=2639) to receive celecoxib 400 mg or placebo once daily for 2 yr. No evidence of benefit in terms of disease-free survival (HR 0.97, 95% CI 0.8–1.17, P=0.75) was observed.[85] In another RCT among patients with Stage 3 colorectal cancer (n=2526), the addition of celecoxib for 3 yr, compared with placebo, to standard adjuvant chemotherapy did not significantly improve disease-free survival (HR 0.86, 95% CI 0.72–1.04, P=0.13).[86] A combination of pre- intra- and postoperative administration of NSAIDs remains to be properly investigated.

Overall therefore, despite a promising signal from small pilot studies, postoperative administration of NSAIDs and beta blockers, even if continued for weeks after cancer surgery, has shown no benefit on oncologic outcomes in sufficiently powered trials.

Dexamethasone

Dexamethasone is used in cancer patients to attenuate the side-effects of chemotherapy and also as a preventative antiemetic during anaesthesia, and has been shown to reduce the incidence of postoperative nausea and vomiting (PONV). However, immunosuppressive actions of glucocorticoids have been raised as a potential risk to their use in oncology patients. *In vitro* studies highlighted that the use of glucocorticoids in oncology may inadvertently enhance cell proliferation and metastasis in some tumour cell lines.[87] An observational study reviewed 2729 patients who had breast cancer surgery, who received either a single dose of 4 mg intraoperative dexamethasone or not. When the n=236 patients who received dexamethasone 4 mg were propensity matched with n=236 patients who did not, there was no significant association in postoperative recurrence (HR 1.38; 95% CI 0.90–2.13) or mortality (HR 1.50; 95% CI 0.88–2.56).[88] In contrast, another retrospective study of >30 000 patients undergoing solid tumour resection suggested that dexamethasone was in fact associated with a reduction in risk of recurrence-free survival (odds ratio 1.28, 95% CI 1.18–1.39).[89] In light of these conflicting results from observational studies, only a well-powered RCT involving thousands of patients can unequivocally determine if there is a causal link between dexamethasone use perioperatively and cancer recurrence. At present, there seems to be insufficient scientific rationale to justify undertaking such a costly and laborious undertaking.

Dexmedetomidine

Dexmedetomidine is a centrally acting alpha-2 adrenergic agonist, which is most commonly used as an analgesic, sedative, or a sympatholytic. It could theoretically have potential to promote recurrence and metastasis, because some cancer cells express alpha-2 adrenoceptors. An *in vivo* and *in vitro* laboratory study showed that unlike midazolam, dexmedetomidine promoted lung carcinoma and neuroglioma cell growth at high doses.[90] Whereas a small retrospective study using clonidine showed reassuring data in breast and lung cancers, with no differences in terms of disease-free survival and overall survival,[91] an underpowered RCT of dexmedetomidine infusion *vs* placebo during anaesthesia and 24 h postoperatively in n=100 patients undergoing uterine cancer

surgery showed that 2-yr follow-up rates of cancer recurrence (16.3% *vs* 8.7% P=0.227) and death (6.7% *vs* 2.2%, P=0.318) were comparable.[92] Most recently however, a follow-up analysis of an RCT of n=620 older cancer surgical patients originally designed with a non-cancer primary endpoint found a benefit of dexmedetomidine infusion during anaesthesia on recurrence-free survival and event-free survival. Median follow-up time was 42 months. Whereas overall survival did not differ, there were 49/309 (16%) deaths with dexmedetomidine *vs* 63/310 (20%) with placebo (adjusted HR 0.78, 95% CI 0.53–1.13, P=0.187), recurrence-free survival was improved with dexmedetomidine (68/309 [22%] events with dexmedetomidine *vs* 98/310 [32%] with placebo; adjusted HR 0.67, 95% CI 0.49–0.92, P=0.012). Event-free survival was also improved with dexmedetomidine (120/309 [39%] events with dexmedetomidine *vs* 145/310 [47%] with placebo; adjusted HR 0.78, 95% CI 0.61–1.00).[93] Although this is encouraging, confirmation of this finding in another RCT where oncologic outcome is the primary endpoint is warranted.

Ketamine

Ketamine is a phencyclidine derivative and is a potent analgesic increasingly used for both acute and chronic pain management. Its mechanism of action is competitive antagonism to N-methyl-D-aspartate (NMDA) receptors located in the dorsal horn of the spinal cord.[94] Subanaesthetic doses of ketamine are used for the management of acute perioperative pain. Typically, this ranges between 0.25 and 1.0 mg kg^{-1} bolus sometimes followed by a continuous infusion of 1.2 mg kg^{-1} h^{-1}.[95] A Cochrane analysis highlighted that as an adjuvant analgesic agent,[96] it reduces postoperative pain and opioid consumption.

The theoretical concept of ketamine modulating immune function and therefore tumorigenesis arises from experimental studies, which demonstrated that ketamine suppressed important pro-inflammatory cytokines that promote tumour production and metastasis, including IL-6, IL-8, and TNF-α production.[97,98]

Separately, it has been demonstrated that CD4+ T-helper lymphocyte (Th) cells have a role in immune protection, including antitumour immunity.[99] These cells consist of two subsets, Th1 and Th2. A recent experimental study highlighted that patients diagnosed with colorectal cancer exhibit a decreased ratio of Th1/Th2. This imbalance inhibits the host's immunological response to the tumour and in turn facilitates metastasis. A study has shown that whereas morphine further decreases this ratio, ketamine shifted the balance towards Th1 cells, suggesting that ketamine may potentially have a protective immunoregulatory mechanism in patients with colorectal cancer.[100] Nevertheless, it is worthwhile noting that experimental data suggest that ketamine significantly suppresses NK cell activity and therefore could promote tumour metastasis.[101]

Two recent large retrospective studies in patients with early-stage lung adenocarcinoma and renal cell carcinoma[67,102] found an association between the use of ketamine as an analgesic and reduced perioperative opioid consumption. Multivariable analysis found that ketamine as an analgesic adjuvant therapy was associated with improved recurrence-free survival in both renal cell carcinoma (HR 0.4, 95% CI 0.16–1.00; P=0.050)[78] and in lung adenocarcinoma (HR 0.44, 95% CI 0.24–0.80; P=0.007).[102] A recent RCT assigned 100 patients undergoing colorectal surgery to a control or ketamine group. There were equivalent findings on postoperative NK cell activity and pro-inflammatory cytokine levels. The incidence of cancer recurrence or metastasis within 2 yr after surgery were the same between the ketamine and control groups. However, this study was not statistically powered to examine oncologic outcome.[103]

The immunomodulatory effects of ketamine may depend on the tumour type, stage, and grade. Robust evidence on whether it might influence long-term oncologic outcome, as for all perioperative drugs, requires a large RCT to determine a truly causal effect on cancer outcomes.

In summary, although the initial anaesthetic technique to be tested for its effect on oncologic outcome after tumour resection, namely regional anaesthesia, has now been conclusively shown to be neutral, other anaesthetic techniques and perioperative interventions warrant continuing investigation. Although the balance of evidence in the propofol *vs* volatile anaesthesia debate is currently also tilting towards neutral, the VAPOR-C trial should provide definitive answers to this and whether lidocaine influences oncologic outcomes. New areas of investigation include how our interventions influence patient-specific tumour genomic expression and tumour-specific subtypes. In particular, we identified a lack of data regarding potential mechanisms involved in these effects, which means that we need more studies to identify biomarkers, possibly useful to stratify patients, identify and explain effects, and conduct efficient translational research projects leading to better outcomes after cancer surgery.

Authors' contributions

Conception and design of the study: DJB
Analysis and interpretation of data: DJB, OM, PF, DM
Drafting the article or revising it critically for important intellectual content: DJB, OM, PF, DM
Final approval of the version to be submitted: DJB, OM, PF, DM

Declaration of interest

PF is a member of the associate editorial board of the *British Journal of Anaesthesia*. The other authors declare that they have no conflicts of interest.

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