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Can Anaesthetic and Analgesic Techniques for Cancer Surgery Affect Cancer Recurrence and Metastasis?

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Abstract Cancer is a leading cause of morbidity and mortality. Surgical resection of primary tumours may be curative; however, mortality from metastasis remains high. Metastasis is a complex process and cancer cells need to evade the host's immune system and the ability to proliferate, migrate, invade adjacent tissues and angiogenesis, in order to successfully metastasise. At the time of surgery, a number of conflicting factors may influence the development of tumour metastases. Recently, it has been hypothesized that perioperative factors including anaesthetic and analgesic techniques could affect metastasis after cancer surgery. This review summarises the current evidence supporting and refuting this hypothesis from experimental, animal and retrospective clinical studies. The results of ongoing, prospective clinical trials are required before a causal effect of anaesthetic–analgesic technique on metastasis can be proven.

Keywords Anaesthesia · Cancer · Metastases · Regional anaesthesia · Recurrence

Introduction

Worldwide, cancer remains one of the leading causes of morbidity and mortality. This is despite the fact that there have been significant advances in surgical and oncological therapies for the treatment of cancer. In the US, it is the second most common cause of death, exceeded only by heart disease. It is estimated that in 2014, 585,720 people in America died of cancer [1]. In the UK, more than one in three people will develop some form of cancer in their lifetime. In 2011, in the UK, there were 331,000 people diagnosed with cancer [2]. In Europe, there are more than 1.7 million deaths a year related to cancer [3]. Whilst the 5-year survival rate for cancer has improved from 49 % in 1975–1977 to 68 % in 2003–2009, mortality related to cancer remains significant. Surgical excision remains the mainstay of treatment for solid tumours; however, cancer metastasis is common and accounts for 90 % of deaths related to solid tumours [4]. Therefore, reducing the incidence of recurrence after primary presentation is an obvious goal of cancer management.

In 2006, it was hypothesized for the first time that anaesthesia, analgesia and perioperative factors might affect cancer metastasis and the balance of evidence from recent literature would suggest that a number of perioperative factors may be important in the long-term outcome after cancer surgery [5•]. A recent consensus conference statement from the BJA highlighted this issue as one of the most important research topics in the area of anaesthesia and perioperative medicine and the importance of funding for future randomized controlled trials.

In this article, we summarise current thinking on the theoretical basis of metastasis and review the available evidence around the hypothesis that anaesthetic and analgesic technique influences outcomes after cancer surgery.

Mechanism of Cancer Metastasis

The term metastasis is defined as "the transfer of disease from one organ or part to another not directly connected to it". Tumour metastasis is a complex multistage process

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during which malignant cells spread from the primary tumour to distant organs. In certain circumstances, only a few cancer cells can successfully colonize metastatic sites; however, metastasis resistant to therapy is the major cause of death from cancer [6]. To successfully metastasise, cancer cells need the following biological characteristics: Evasion of normal cell apoptosis, evasion of host immune rejection, adaption to adverse growth conditions [7], invasion through physical cellular barriers and angiogenesis.

The process of metastasis is a series of linked steps involving the transformation of a single cell to tumour cells by multiple cycles of division and mutations thus making them genetically unstable [8]. Cells then evade apoptosis and establish an independent blood supply mediated by vascular endothelial growth factor and prostaglandin E2 [9–11]. Normal surrounding stroma and tumour-associated vasculature are invaded by cancer cells [4, 12], these cancer cells then migrate to distant organs in the circulatory system where they arrest in capillary beds, migrate into organ parenchyma, proliferate and establish their own independent blood supply.

Role of the Immune System and Its Defence Against Tumour Cells

Natural killer (NK) cells and cytotoxic T cells play a major role in the defence against cancer, and an intact cellular immune system is responsible for the hosts defence against developing neoplasms [13]. NK cells are a subpopulation of lymphocytes that discriminate between self and non-self and kill virally infected cells and tumour cells [14]. Lower levels of the cytotoxic activity of NK cells have been demonstrated in patients with higher levels of circulating tumour cells and this correlates with poorer prognosis [15••]. In animal studies, stress-induced suppression of NK cell activity has been demonstrated to enhance tumour development [16]. In a rat model, suppression of NK cell activity with anaesthetic agents has resulted in an increase in lung metastasis [17]. Developing tumours induce a pro-inflammatory state and cells and cytokines that mediate chronic inflammation can facilitate tumour initiation and metastasis [18]. Prostaglandins, which are synthesized by inflammatory cells may also facilitate metastatic progression in cell culture models [19] (Table 1).

Cancer cells may evade the host's immune response, thus leading to tumour progression. This can be as a result of the loss of expression of specific antigens that would normally elicit an immune response [20]. Altered expression of major histocompatibility complex (MHC) class I antigen plays an important role in tumour evasion of the immune system. This alteration allows tumour cells to go unrecognised by T lymphocytes and facilitates escape from anti-tumour immune mechanisms [21]. The absence of expression of co-stimulators has been shown to cause tumour escape, as co-stimulators are required for activation of T cell response [22]. Ectopic expression of specific ligands may also result in rejection of tumours by NK cells [23].

The Effect of Surgery on Host Defence Mechanisms and Metastasis

Surgical excision is one of the primary treatments for most solid tumours. In the case of localized disease, primary excision may be curative [24]. However, following successful surgical excision occult neoplastic disease can still remain, known as minimal residual disease (MRD) [25]. Since 1950s, it has been noted that surgical manipulation of a tumour can result in dissemination of the disease [26]. In rat models, laparotomy and thoracotomy have been shown to enhance tumour load [27]. Several theories explain how surgery may promote the formation of metastases following surgery.

Current Evidence for Effect of Anaesthesia on Cancer by Drug Category

It is suggested that if the perioperative period is a critical time in the development of metastasis, there may be a window of opportunity in the perioperative period in which anaesthetists can intervene to alter the balance of forces in favour of resisting cancer metastasis [16, 34]. Below we discuss the evidence surrounding common drugs used in anaesthetic practice and how they may influence cancer metastasis.

Intravenous Anaesthetic Induction Agents

Common IV induction agents include propofol, ketamine and thiopentone. The effects of these agents have been studied in an inoculation animal model of breast cancer. In one study, rats were injected with propofol, ketamine or thiopentone, and NK cell activity and resistance to metastasis were measured. All agents except propofol reduced NK cell activity and increased lung metastases [17]. In a cell culture study, prostate cancer cells were exposed to propofol and isoflurane. The results found that propofol inhibited hypoxia-inducible factor-1α activation and partially reduced cancer cell malignant activities [35••]. An in vitro study carried out on breast cancer cells demonstrated that propofol reduced the expression of the neuroepithelial cell transforming gene 1 (NET1), which is associated with promoting migration in adenocarcinoma in vitro and propofol also reduced cell migration in ER-positive and -negative breast cancer cells [36••]. In a retrospective analysis of 2838 patients who underwent

Table 1 Surgical influence on metastasis

Proposed mechanism	Supporting evidence 1	Supporting evidence 2
Dispersal circulating cancer cells (CCC)—attributable to handling and disruption of tumour [16]	CCC increased postoperatively in lung cancer patients. Increase correlated with extent of parenchymal manipulation [28]	CCC detected in peripheral blood in colorectal cancer resection patients postoperatively—suggesting haematogenic tumour cell dissemination enhanced by surgical manipulation [29]
Suppression cell-mediated immunity [18, 30]	Inoculation murine model—surgical group demonstrated greater tumour load than GA only group. Blockage of sympathetic stimulation by propranolol resulted in suppression of effects of surgical stress on tumour growth [31]	NK cell dysfunction demonstrated in humans following surgery [32]
Increased concentrations of proangiogenic factors i.e. vascular endothelial growth factor (VEGF) [31]	Elevated levels VEGF postoperative mastectomy patients [33•]	

surgery for breast, colon or rectal cancer, there was no statistically significant difference and randomized controlled trials were recommended [37].

Inhalation Agents

In an experimental animal model, the volatile agents isoflurane and halothane have been studied. Mice injected with melanoma cells had an increased number of pulmonary metastases when exposed to halothane or isoflurane compared to the control group [38]. In vitro studies have demonstrated effects of volatile agents that may affect cancer metastasis [35••, 39]. A study investigating the effects of isoflurane and propofol on prostate cancer cell lines demonstrated that cells exposed to isoflurane expressed upregulation of hypoxia-inducible factor 1-α (HIF-1α) and enhanced malignant potential. Propofol was found to inhibit activation of HIF 1-α and cancer cell malignant activities as discussed above [35••]. An in vitro study examining the effects of sevoflurane, isoflurane and desflurane on human T lymphocytes concluded that sevoflurane and isoflurane induced apoptosis in human T lymphocytes in a dose-dependent manner. In contrast, desflurane had no effect on apoptosis on T lymphocytes [40]. An in vitro study on colon cancer cells demonstrated that brief exposure to isoflurane leads to resistance to apoptosis in cancer cells [41]. Recently, a study carried out on human breast adenocarcinoma cells examined the effects of xenon and sevoflurane on migration and expression of angiogenesis biomarkers in breast cancer cells. The study concluded that xenon decreased the release of the proangiogenic factor regulated on activation normal T cell expressed and secreted (RANTES) and also reduced migration of breast adenocarcinoma cells [42].

Nitrous Oxide

Nitrous oxide (N_2O) interferes with vitamin B_{12} and folate metabolism, it impairs DNA formation and new cell formation and may affect immunosuppression. Despite this scientific basis for potential harm with nitrous oxide, clinical studies have not shown major adverse effects [43, 44]. The ENIGMA-II trial supported the safety profile of N_2O. ENIGMA-II studied the effects of N_2O on patients undergoing major non-cardiac surgery. Over 7000 patients were randomized to receive N_2O or not to receive N_2O as part of their GA. The primary outcome of the study was death and cardiovascular complications within 30 days of surgery. The results demonstrated no increase in the risk of death and cardiovascular complications with the use of N_2O [45]. No human studies have demonstrated an adverse effect of N_2O on cancer recurrence. A follow-up analysis of a previous randomized trial of patients who underwent anaesthesia and surgery for colorectal cancer found no significant difference in cancer recurrence between patients who received 65 % N_2O or nitrogen. The follow-up time period was 4–8 years [46].

Local Anaesthetics

Local anaesthetics (LA) exert their analgesic effect by acting on voltage-gated Na^+ channels on nociceptive neurons. Cancer cells, including breast, prostate and colon cancer cells also express local anaesthetic sensitive voltage-gated Na^+ channels. A recent cell study examined the effects of ropivacaine on voltage-gated Na^+ channels on colon cancer cells. It concluded that ropivacaine inhibited voltage-gated Na^+ channel activity and metastatic colon cancer cell invasion thus implying that the use of amide LA may be beneficial in cancer surgery. Further, Hales and

colleagues demonstrated that a particular subtype of voltage activated Na^+ channels, the variant $Na_v1.5$, which is present and expressed by colon cancer cells, is susceptible to inhibition by amide LA [47••]. In vitro studies of breast cancer cells have demonstrated that lidocaine and ropivacaine demethylate cancer cell deoxyribonucleic acid (DNA). This may result in reactivation of tumour suppressor genes and inhibition of tumour growth. The study also demonstrated that the demethylating effects were enhanced when lidocaine was used in combination with the chemotherapy agent 5-aza-2′-deoxycytidine. Bupivacaine was also studied but found to have no effect on breast cancer cells [48••]. Similarly, an in vitro study of breast cancer cells found that bupivacaine had no effect on neuroepithelial cell transforming gene 1 (NET1). The NET1 gene is associated with promoting migration in adenocarcinoma in vitro [36••]. Beneficial antimetastatic effects of lidocaine and ropivacaine have also been demonstrated in a study of lung cancer cells. In this study, lung cancer cell migration was inhibited by both LAs. This was associated with inhibition of TNFα-induced Src tyrosine protein kinase activation which is important in tumour growth and metastasis [49••]. Laboratory evidence would suggest that the use of LA in the perioperative period might have a beneficial role and the results of clinical trials are awaited.

Opioids

Opioids are commonly used in the perioperative and postoperative period in the management of acute pain. Morphine, one of the most widely used opioids, acts via μ-opioid receptors (MOR) in the central nervous system and thus produces its analgesic effect. The MOR are also found in peripheral organs and tissues [50]. Recently, published retrospective clinical studies have suggested that an opioid sparing anaesthetic technique may reduce the risk of cancer recurrence [34, 51, 52]. Studies have demonstrated that opioids may adversely affect cellular immunity including NK cell function. NK cells play a major role in the defence against cancer. In an inoculation rat model of cancer, administration of high-dose fentanyl demonstrated a significant suppression of NK cell cytotoxicity and an increase in tumour metastasis [53]. In humans, opioids have also been shown to suppress NK cell cytotoxicity [54].

Live animal studies of a transgenic mouse model have demonstrated that morphine can lead to the promotion of angiogenesis, tumour growth and metastasis by activation of certain signalling pathways including cyclooxygenase-2 [55••]. It has also been demonstrated that morphine increases levels of inflammatory mediators such as cytokines and substance P and that this may effect tumour progression.

In several types of human non-small-cell lung cancer (NSCLC), the MOR are upregulated [56, 57]. In human breast adenocarcinoma opioid receptors, the MOR are expressed in cancer cells [58]. In a study examining lung tissue samples from patients with lung cancer, there was a significant increase in the expression of the MOR in cancer samples. Further, samples from patients with metastatic lung cancer had a twofold increase in MOR expression ($p = 0.0013$) [59••]. In patients with metastatic prostate cancer, higher MOR expression and greater opioid requirements have been associated with a shorter progression-free survival and overall survival [60]. A single-centre retrospective analysis of 99 patients who underwent video-assisted thoracoscopic surgery with lobectomy for Stage I or IIa NSCLC found a relationship between patients who received higher total doses of opioids in the first 96 h postoperatively and recurrence of their lung cancer at 5 years [61••].

It has also been demonstrated that μ-opioid receptor agonists stimulate urokinase plasminogen activator secretion in breast cancer cell lines. Urokinase plasminogen activator is used as a marker in cancer prognosis and is involved in increasing tumour cell invasion and metastasis. The study, however, did not find any direct increase in cancer cell proliferation [50].

In contrast, morphine analgesia has been shown to suppress tumour growth and metastasis in a mouse model. In a study of mice inoculated with melanoma cells into the hind paw, both lung metastasis and tumour growth were inhibited by administration of morphine. The study suggested this was as a result of relief of cancer pain [62].

Taken together, the balance of available evidence suggests that the use of opioids may influence cancer metastasis and that an opioid sparing anaesthetic technique may be beneficial. However, without the results of randomized controlled trials, recommendations on changing anaesthetic technique cannot be made.

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that inhibit the activity of the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Prostaglandins are inflammatory mediators which may promote cancer cell proliferation, invasion and alter the immune system response to tumour cells [63]. COX-2 is the major enzyme involved in the synthesis of prostaglandins from arachidonic acid [64]. Increased expression of COX-2 has been demonstrated in 90 % of lung tumours, 71 % of colon adenocarcinomas and 56 % of breast tumours [63, 65]. In breast cancer, COX-2 expression has been shown to be associated with angiogenesis, increased cell motility, invasion and metastases [66, 67].

An in vitro study of breast cancer cells examined the effects of the COX inhibitors, aspirin, ketorolac and celecoxib and of the lysine antifibrinolytics, 1-aminocaproic acid and tranexamic acid on extracellular matrix (ECM) proteases associated with breast cancer cells. ECM proteases are important in the regulation of tumour invasion, growth and migration. The study found that both the antifibrinolytics and COX inhibitors had mixed effects on ECM proteases and that further animal and experimental studies would be warranted to investigate the effect of these changes [68••].

An observational study of over 80,000 postmenopausal women found that regular use of aspirin, ibuprofen and other NSAIDs may have a significant protective effect against the development of breast cancer [69]. A review of 91 epidemiologic studies found that daily intake of NSAIDs (mainly aspirin) reduced risk of colon, breast, lung, prostate, oesophageal, gastric and ovarian cancer [70]. Analyses of seven randomized trials (22,253 patients) studying the effects of daily aspirin on vascular events demonstrated a reduction in the risk of death for all solid cancers ($p < 0.0001$). The benefit of daily aspirin increased with duration of treatment [71]. A retrospective study of 720 patients undergoing conservative breast cancer surgery found that patients who received an intraoperative NSAID (ketorolac or diclofenac) had an improved disease-free survival and an improved overall survival. A prospective, randomized trial is underway to investigate if these associations are causative (NCT01806259) [72]. Neutrophil:-lymphocyte ratio (NLR) has been identified as a prognostic indicator in cancer. An observational study of early breast, renal and lung cancer demonstrated that a higher NLR was associated with a higher risk of relapse and mortality and that the intraoperative use of NSAIDs was associated with a reduced recurrence rate and lower mortality [73].

Whilst there is some observational study evidence to suggest that daily use of NSAIDs is associated with a risk reduction of developing a number of malignancies, without the results of a prospective randomized trial into the use of perioperative NSAIDs and their effect on cancer recurrence, conclusions cannot be drawn.

Glucocorticoids

Glucocorticoids are widely used in cancer patients and studies have demonstrated beneficial and negative effects associated with them. A systematic review of the effects of glucocorticoids on non-hematologic malignancy demonstrated that in breast and prostate cancer there may be a benefit but in lung cancer a deleterious effect may occur [74]. Dexamethasone has been shown to suppress tumour angiogenesis in prostate cancer cells by decreasing VEGF and interleukin 8 [75]. In anaesthetic practice, the glucocorticoid dexamethasone is commonly used as an anti-emetic. A subgroup analysis of a randomized clinical trial studying the effects of 8 mg of IV dexamethasone on 60 patients undergoing elective colectomy for colon cancer was carried out with a follow-up time of 5 years. The results demonstrated that there were no differences between the placebo and the dexamethasone group for overall or disease-free survival but in the dexamethasone group there was a statistically significant higher rate of distant recurrence ($p = 0.04$). Due to the small sample size, the results should be interpreted with caution and randomized controlled trials will be necessary to determine if these observations are causative or not [76].

Translational Studies in Regional Anaesthesia

While awaiting data from randomized controlled trials, which require large numbers of patients and a minimum 5 year post-enrolment follow-up, one model for evaluating the possible overall effect of anaesthetic–analgesic technique on cancer cells is to use serum from patients randomized to receive different anaesthetic techniques on breast cancer cell and immune biology in vitro. A number of recently published translational studies have examined the effects of a regional technique, specifically the use of paravertebral blocks combined with total intravenous anaesthesia (TIVA) on the effects of serum from breast cancer resection patients. Women undergoing primary breast cancer surgery were randomized to receive a propofol-paravertebral block (PPA) anaesthetic technique or a sevoflurane-opioid (GA) technique as part of an ongoing prospective trial (NCT 00418457). Serum donated from these patients preoperatively and postoperatively was examined to investigate the effects of anaesthetic technique on apoptosis in oestrogen receptor (ER)-negative breast cancer cells. This study concluded that in patients who received a GA technique there was a greater reduction in apoptosis in ER-negative breast cancer cells than in the PPA group. Resistance of apoptosis is an essential ability of tumour cells and an important step in the process of metastasis and if anaesthetic technique affects cancer cell apoptosis it may also have an impact on tumour metastasis [77••]. Previous in vitro studies of breast cancer cells have demonstrated inhibited proliferation but not migration of ER-negative breast cancer cells when a regional technique (PPA) was used compared to a GA technique [78]. In a prospective, randomized study of 30 women undergoing a mastectomy for breast cancer, the addition of a regional technique in the form of a continuous paravertebral infusion demonstrated a reduction in the stress response to surgery but no effect on the angiogenic factors, vascular endothelial growth factor or prostaglandin E_2 [10]. In contrast, a study evaluating the effects of a propofol-

epidural anaesthesia (PEA) technique in colon cancer surgery patients found that concentrations of serum angiogenic factors including VEGF were reduced in the PEA group compared to the general anaesthesia alone group [79•]. Reduction in serum VEGF and transforming growth factor β has also been demonstrated in patients who received PPA technique compared to GA and opioid technique in breast cancer surgery patients [33•]. Serum from patients undergoing breast cancer surgery who received a PPA anaesthetic technique has demonstrated greater human donor NK cell cytotoxicity compared with serum from patients who received a GA technique [80••].

Retrospective Clinical Studies in Regional Anaesthesia

Supplementation of general anaesthesia with a regional technique may attenuate the immunosuppressive effects of surgery. Regional techniques will reduce opioid requirements and lower the perioperative requirements for volatile anaesthetic agents [54]. These effects are beneficial as NK cell function will be preserved and there may be a resultant reduction in metastatic spread of cancer [5•]. However, the results of retrospective trials and in vitro studies are conflicting.

Retrospective studies have demonstrated the possible beneficial effects of regional anaesthetic techniques on cancer recurrence. In a large retrospective analysis, patients who were treated for prostate adenocarcinoma by radical prostatectomy and received GA in combination with neuraxial anaesthesia ($n = 1642$) were matched 1:1 with patients who had GA alone based on age, surgical year, pathological stage, Gleason scores and the presence of lymph node disease. The results demonstrated that GA alone was associated with an increased risk of prostate cancer progression compared to the group that received GA combined with a neuraxial technique [81]. Beneficial effects of regional techniques on cancer recurrence have also been demonstrated in retrospective studies of patients undergoing laryngeal and hypopharyngeal cancer surgery who received cervical epidural analgesia [82], in patients who underwent percutaneous radiofrequency ablation of small hepatocellular carcinomas [83], in ovarian cancer surgery patients [84] and in breast cancer patients under epidural analgesia [5•]. A large retrospective analyses ($n = 42{,}151$) of patients who underwent an open colectomy for non-metastatic colorectal cancer found that epidural use was associated with improved survival but not associated with a decrease in cancer recurrence [85••]. Similar trends toward improved survival were demonstrated in patients undergoing surgery for malignant melanoma who received spinal anaesthesia [86] and in patients who had surgery for ovarian adenocarcinoma and received epidural analgesia [87].

Conflicting results have been reported in other retrospective studies of patients undergoing surgery for prostate and colon cancer where no difference in cancer recurrence or survival was associated with the use of a regional technique [18, 88–91].

Follow-Up Analysis of Randomized Controlled Trials in Regional Anaesthesia

In follow-up analyses of a previously published trial, a survival benefit was associated with the use of epidural anaesthesia compared to GA alone in patients who underwent surgery for non-metastatic colon cancer [92]. A secondary analysis of a randomized controlled trial of patients undergoing radical prostatectomy who were randomized to GA alone or a combined GA/epidural anaesthesia group observed no difference between the 2 groups in disease-free survival with a median follow-up time of 4.5 years [93]. The conflicting results of published trials (Table 2) and the retrospective design of the studies discussed highlights the need for future prospective randomized controlled trials before recommendations to alter anaesthetic practice can be made.

Other Perioperative Factors

Other perioperative factors such as blood transfusion, hypothermia and inspired oxygen fraction have been postulated to affect cancer recurrence.

Effect of Blood Transfusion

Allogeneic blood transfusions have an immunosuppressive effect. This effect may be associated with increased cancer recurrence. A meta-analysis investigating the influence of perioperative blood transfusions on colorectal cancer recurrence found a consistently adverse association [97]. A similar meta-analysis examining the impact of perioperative blood transfusions on patients undergoing surgical resection of lung cancer did not establish a conclusive effect [98]. In a study of patients undergoing surgery for rectal cancer, distant metastases rates and disease-free survival were not influenced by perioperative blood transfusion [99]. A retrospective review of 1710 patients who underwent curative gastrectomy for gastric cancer demonstrated a dose–response relationship between the amount of perioperative transfused blood and prognosis. On multivariate analysis, transfusion was shown to be an independent risk factor for recurrence [100].

Table 2 Summary of retrospective clinical evidence of regional anaesthesia and cancer recurrence

Type of study	Reference	Surgery	Technique	Outcome
Retrospective	Exadaktylos et al. [5•]	Mastectomy and axillary clearance for breast cancer	GA + PVAA ($n = 50$)	Fourfold decrease in cancer recurrence in PVAA group. 2.5–4 year follow-up
			GA + opioid analgesia ($n = 79$)	
Retrospective	Biki et al. [94]	Radical prostatectomy for prostate carcinoma	GA + thoracic epidural analgesia ($n = 102$)	57 % reduction in cancer recurrence in epidural group, $p = 0.012$
			GA + opioid analgesia ($n = 123$)	Recurrence defined as increase in PSA
Retrospective	Wuethrich et al. [88]	Radical prostatectomy for localized prostate carcinoma	GA + thoracic epidural ($n = 103$)	Increase in clinical progression-free survival ($p = 0.009$) in epidural group
			GA + ketorolac + opioid analgesia ($n = 158$)	No difference in biochemical recurrence-free survival ($p = 0.42$), cancer-specific survival ($p = 0.9$), or overall survival ($p = 0.9$)
Retrospective	Ismail et al. [95]	Brachytherapy for cervical cancer	Neuraxial anaesthesia ($n = 69$)	No difference in tumour recurrence ($p = 0.526$) or survival ($p = 0.537$)
			GA ($n = 63$)	
Retrospective	Gottschalk et al. [18]	Open colectomy	GA + epidural group ($n = 256$)	No difference in cancer recurrence except in patients >64 year. Follow-up 1.8 year
			GA + opioid analgesia ($n = 253$)	
Retrospective	Gupta et al. [89]	Open colectomy	GA + epidural ($n = 562$)	GA + opioid group had higher mortality rate in rectal cancer ($p = 0.049$)
			GA + PCA opioid analgesia ($n = 93$)	No difference with colon cancer ($p = 0.23$)
Retrospective	Lin et al. [87]	Laparotomy for ovarian carcinoma	Epidural anaesthesia + analgesia ($n = 106$)	Epidural group had improved 3 year survival and 5 year survival rates ($p = 0.043$)
			GA + opioid analgesia ($n = 37$)	
Retrospective	De Oliviera et al. [84]	'Debulking' surgery for ovarian cancer	Epidural ($n = 55$)	Intraoperative epidural analgesia associated with reduced risk of cancer recurrence
			Opioid analgesia ($n = 127$)	
Retrospective	Lai et al. [83]	Radiofrequency ablation of hepatocellular carcinoma	Epidural or GA hazard ratio for disease-free survival = 3.66, $p = 0.001$	GA associated with increased recurrence-free survival
				No difference in overall survival
Retrospective	Day et al. [90]	Laparoscopic colorectal resection for adenocarcinoma	Epidural ($n = 07$)	No difference in overall ($p = 0.622$) or disease-free survival at 5 year ($p = 0.490$)
			Spinal ($n = 144$)	
			Morphine PCA ($n = 173$)	
Retrospective	Gottschalk et al. [86]	Lymph node dissection for malignant melanoma	Spinal anaesthesia ($n = 52$)	Non-significant trend towards improved cumulative survival rate in spinal anaesthesia group ($p = 0.087$)
			GA-sevoflurane/sufentanil ($n = 118$)	
			GA-propofol/remifentanil total i.e. anaesthesia ($n = 103$)	
RCT (follow-up)	Christopherson et al. [92]	Open colectomy for colorectal cancer	GA + epidural analgesia ($n = 85$)	Early survival benefit (for up to 1.46 year) in epidural group ($p = 0.012$)
			GA + opioid analgesia ($n = 95$)	No benefit if metastatic disease present
RCT (follow-up)	Tsui et al. [93]	Radical prostatectomy	GA + epidural analgesia ($n = 49$)	No difference in disease-free survival ($p = 0.44$)
			GA + opioid analgesia ($n = 50$)	4.5 year follow-up

Table 2 continued

Type of study	Reference	Surgery	Technique	Outcome
RCT (follow-up)	Myles et al. [96]	Major abdominal surgery, subgroup analysis of patients with colorectal cancer	GA + epidural analgesia ($n = 230$) GA + opioid analgesia ($n = 216$)	No difference in cancer recurrence-free survival ($p = 0.61$) or recurrence –free survival ($p = 0.61$) Recurrence and mortality rates at 5 year also similar
Retrospective population	Cummings et al. [85••]	Open colectomy for non-metastatic colorectal cancer	Epidural analgesia ($n = 9670$) Opioid pain management ($n = 32{,}481$)	61 % 5-year survival with epidural vs. 55 % opioid ($p < 0.001$). No difference in cancer recurrence rates ($p = 0.28$)
Retrospective	Wuethrich et al. [91]	Radical prostatectomy for prostate carcinoma	GA + epidural analgesia ($n = 67$) GA + ketorolac + opioid analgesia ($n = 81$)	No difference in overall survival ($p = 0.07$), cancer-specific survival ($p = 0.32$), local recurrence free ($p = 0.75$) or distant recurrence-free survival ($p = 0.18$)
Retrospective	Merquiol et al. [82]	Larynx or hypopharynx cancer surgery	GA + cervical epidural ($n = 111$) GA + opioid analgesia ($n = 160$)	GA + epidural group increased overall survival ($p = 0.03$) and increased cancer-free survival ($p = 0.04$)
Retrospective	Scavonetto et al. [81]	Radical prostatectomy for prostate carcinoma	GA + neuraxial analgesia ($n = 1642$) GA alone ($n = 1642$)	GA alone increased risk systemic progression ($p = 0.008$) and overall mortality ($p = 0.047$)

PVAA paravertebral anaesthesia and analgesia [51]

Effect of Perioperative Hypothermia

Detrimental effects of perioperative hypothermia are well established. Increase in perioperative blood loss secondary to impaired coagulation and platelet dysfunction, postoperative wound infections and delay in recovery from anaesthesia are recognized complications associated with even mild perioperative hypothermia. Hypothermia also adversely effects cell-mediated immunity [101, 102]. In a follow-up analysis of a study investigating the effects of perioperative hypothermia on wound infections, no association was demonstrated between hypothermia and cancer recurrence [103]. However, given the known adverse effects associated with perioperative hypothermia it should be avoided.

Effect of Inspired Oxygen Fraction

The effect of supplemental perioperative oxygen on the incidence of surgical wound infections has been studied in a number of randomized controlled trials [104, 105]. Hyperoxia may lead to angiogenesis and DNA damage, which could impact tumour development. A recent post hoc analysis of the PROXI trial was carried out to investigate if a high (80 %) perioperative inspired oxygen fraction was associated with a risk of new or recurrent cancer. The PROXI trial randomized 1386 patients who underwent emergency or elective laparotomy to receive a perioperative inspired oxygen fraction of either 80 or 30 %. The primary outcome was surgical site infection at 14 days. In this post hoc analysis, an association between inspired oxygen and cancer incidence or recurrence was evaluated with a medium follow-up time of 4 years. No difference in the incidence of new or recurrent cancers in either group was detected, although in the 80 % oxygen group a significantly shorter cancer-free survival period was found [106].

Conclusion

Over the last decade, the question as to whether perioperative factors influence cancer recurrence has become one of the most important topics in anaesthesia. Whilst there are a large number of experimental, animal and retrospective studies suggesting a link that there are as of yet no results from ongoing prospective randomized clinical controlled trials (Table 3). The results of these trials are eagerly anticipated, as a positive finding—i.e. reduced cancer recurrence would impact the care of all patients undergoing cancer surgery and potentially reduce the economic cost associated with cancer metastasis, because decreased recurrence rates would reduce the number of patients requiring chemotherapy, radiotherapy and the cost of side effects associated with these treatments. However, results of clinical trials are awaited before changes of routine practice in cancer patients are warranted on a widespread scale. These large-scale, painstaking and time-consuming studies require urgent public and private funding

Table 3 The future—summary of some ongoing prospective, randomized clinical trials [51]

Title	Study design	Intervention	Primary outcome	Location	Estimated completion date
Regional anaesthesia & breast cancer recurrence, NCT00418457	Multi-centre prospective randomized clinical trial $n = 1100$	GA + postoperative opioid analgesia or GA or deep sedation with epidural or paravertebral anaesthesia/ analgesia	Cancer recurrence rate up to 10 years	Mater University Hospital, Ireland Cleveland Clinic, OH, USA Medical University of Vienna, Austria University of Dusseldorf, Germany	March 2015
The effect of adding intraoperative regional anaesthesia on cancer recurrence in patients undergoing lung cancer resection NCT 011799308	Prospective randomized, double-blind trial, $n = 1532$	GA + postoperative opioid analgesia or GA + thoracic epidural analgesia	Disease-free survival up to 5 years	Cleveland Clinic, OH, USA Mater University Hospital, Ireland	August 2018
Epidural or patient-controlled analgesia for colorectal cancer surgery. Long-term outcomes (EPICOL) NCT 01318161	Multi-centre, prospective randomized clinical trial $n = 300$	GA + postoperative opioid analgesia (PCA) or GA + epidural analgesia with local anaesthetic and opioid	Long-term (up to 5 years) all-cause mortality	University Hospital Linköping, Sweden University Hospital Örebro Sweden	December 2018
Regional anaesthesia in colon rectal surgery NCT00684229	Multi-centre, prospective randomized, double-blind trial, $n = 2500$	GA(sevoflurane) + opioid analgesia or GA + epidural anaesthesia/analgesia	Cancer recurrence rate up to 5 years	Cleveland Clinic, OH, USA Hospital Italiano de Buenos Aires, Argentina University of Dusseldorf, Germany	December 2022
Anaesthesia and cancer recurrence in malignant melanoma NCT01588847	Single-centre, prospective, randomized, single blind trial, $n = 230$	GA (sufentanil, propofol, rocuronium & sevoflurane) Or Spinal anaesthesia (Bupivacaine 0.5 %)	Overall survival (up to 5 years)	University Hospital Muenster, Germany	March 2019

to ensure they are expedited to the required standard to deliver evidence based answers to the urgent question of whether anaesthetic and analgesic techniques indeed affect cancer outcomes.

Compliance with Ethics Guidelines

Conflict of Interest Donal J. Buggy has received unrestricted research grants from Air Liquide, manufacturer of the anaesthetic gas xenon; and is an Editorial Board Member for the *British Journal of Anaesthesia*. Laura Marshall declares that she has no conflict of interest. Abdul Hameed Khan declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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