Perioperative events influence cancer recurrence risk after surgery

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Abstract | Surgery is a mainstay treatment for patients with solid tumours. However, despite surgical resection with a curative intent and numerous advances in the effectiveness of (neo) adjuvant therapies, metastatic disease remains common and carries a high risk of mortality. The biological perturbations that accompany the surgical stress response and the pharmacological effects of anaesthetic drugs, paradoxically, might also promote disease recurrence or the progression of metastatic disease. When cancer cells persist after surgery, either locally or at undiagnosed distant sites, neuroendocrine, immune, and metabolic pathways activated in response to surgery and/or anaesthesia might promote their survival and proliferation. A consequence of this effect is that minimal residual disease might then escape equilibrium and progress to metastatic disease. Herein, we discuss the most promising proposals for the refinement of perioperative care that might address these challenges. We outline the rationale and early evidence for the adaptation of anaesthetic techniques and the strategic use of anti-adrenergic, anti-inflammatory, and/or antithrombotic therapies. Many of these strategies are currently under evaluation in large-cohort trials and hold promise as affordable, readily available interventions that will improve the postoperative recurrence-free survival of patients with cancer.

Surgery is the foremost treatment strategy for the majority of patients with solid tumours. However, even when complete locoregional control is thought to have been achieved, postoperative disease recurrence occurs in up to a third of patients and carries a high risk of mortality[1]. The stress response to surgery generally involves the activation of physiological responses that have evolved to promote wound healing after injury. These responses include activation of neural, inflammatory, and pro-angiogenic signalling pathways, which also promote the growth and metastatic spread of cancer. Unsurprisingly, accumulating evidence suggests that these perioperative events lead to disease recurrence by increasing the growth of pre-existing micrometastases or by enabling a residual fraction of tumour cells to progress, resulting in locoregional recurrence or seeding of new metastatic disease[2–4].

Over a century ago, in 1889, Stephen Paget first proposed a 'seed and soil' framework that described metastasis in terms of cancer cell dissemination and colonization in 'fertile soil' (REF. 5). Such an analogy remains highly relevant to the perioperative period, during which both cancer-cell dissemination and perturbations in tissue environments occur. Disruption of the tumour during surgery might release cancer cells — the 'seed' — into circulation[6–8]. Meanwhile, vulnerability to colonization arises from the modulation of immune function and the activation of neural and/or pro-inflammatory signalling, which might then prime both local and distant tissue beds to form a privileged microenvironment (the pre-metastatic niche, or 'soil')[9,10]. This period of vulnerability might feasibly extend to >1 week after surgery and encourage the 'seed' to 'germinate and fertilize', thereby establishing viable minimal residual disease[11,12]. As a consequence, the risk of locally recurrent or metastatic disease following surgery has been documented in numerous tumour types, including breast[13,14], ovarian[15], non-small-cell lung[16], and colorectal cancers[17].

The findings of clinical research suggest that more extensive surgery and the subsequent potential for protracted inflammation, owing to postoperative complications, will further increase the risk of disease recurrence. For example, undergoing an additional invasive reconstructive procedure after breast cancer surgery has been demonstrated to alter both the risk and pattern of cancer recurrence, compared with undergoing a simple mastectomy[18,19]. Postoperative complications such as wound

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Key points

- Surgery remains the primary treatment for patients with solid tumours, yet postoperative locoregional recurrence and distant metastasis occur frequently and confer high risks of morbidity and mortality
- Deleterious effects of surgery include the initiation of local and/or systemic inflammation, increased catecholamine levels, immunosuppression, a prothrombotic state, and exposure to anaesthetic agents; these processes overlap with cancer-promoting signalling pathways
- Cancer cells that escape resection are subject to perioperative physiological changes and might disseminate and colonize distant organs, thus contributing to postoperative cancer recurrence
- Perioperative use of β-adrenoceptor antagonists, anti-inflammatory drugs, intravenous anaesthetics, and antithrombotic agents is linked with improved survival outcomes in patients with cancer
- >60% of patients with cancer are treated with surgery; therefore, offsetting the deleterious effects of surgery by use of affordable and readily available therapies might rapidly improve the postoperative survival of patients with cancer

infection[2,3] or anastomotic leak[4,20] have also been associated with inferior cancer-related outcomes. Alarmingly, the findings of two retrospective clinical studies raise the possibility that the choice of anaesthetic agent might have implications for long-term survival in patients who undergo cancer surgery[21,22]. These data emphasize the vulnerability to recurrence that arises from exposure to certain perioperative events.

The potential magnitude of perioperative vulnerability is underscored by the fact that >60% of the >15 million patients diagnosed with cancer each year will require surgical resection[23] and that >80% of these patients will be exposed to anaesthesia for at least one, if not several curative, diagnostic, or palliative procedures[24]. As such, any opportunity to abrogate cancer risk arising during the vulnerable perioperative period could provide substantial benefits to patients globally. Herein, we discuss the biological processes that underpin perioperative vulnerability to cancer recurrence as well as the accumulating preclinical and clinical evidence that the choice of anaesthetic and/or adjunctive strategy might modulate a patient's risk of cancer recurrence following surgery.

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Pathophysiological response to surgery

Postoperative cancer recurrence frequently takes the form of metastatic disease[13,14]. In the traditional paradigm, the development of metastasis is seen as a late-occurring event in the stepwise, Darwinian-like evolution of cancer. According to this theory, metastases occur only when cells acquire a complementary set of somatic genetic changes that enable dissemination from the primary tumour, entry into the lymphatic or vascular network, survival in the circulation, and an ability to establish malignant growth at distant sites[25]. The 'parallel progression' model challenges this perspective, unifying a series of clinical and experimental observations collectively suggesting that both dissemination to and colonization of distant sites can occur early in the development of a cancer[26]. Early support for this model came from genetic analyses of samples from patients with breast cancer, in whom disseminated tumour cells (DTCs) isolated from bone marrow were found to contain fewer genetic aberrations than their matched primary tumour counterparts[27]. This phenomenon has been captured and mechanistically characterized in animal models of pancreatic cancer[28] and breast cancer[29], in which epithelial-to-mesenchymal transition programmes were found to promote the dissemination of cancer cells early in the course of the disease, which was followed by colonization of distant sites even before the primary tumour had become detectable. In the perioperative context, these findings suggest that cells liberated during surgery, even when originating from very early stage tumours, are able to disseminate and form metastases.

Accumulating evidence indicates that the fate of DTCs is determined by the conditions encountered during transit and at the early stages of colonization. Events during intravascular passage, such as interactions with activated platelets, neutrophils, and endothelial cells, as well as transient exposures to pro-angiogenic signals that are induced by the surgical inflammatory response might improve the efficiency of metastatic outgrowth[25]. Indeed, the pathophysiological response to surgery bears many similarities with conditions that promote cancer progression. Thus, events in the perioperative period could influence the viability and subsequent expansion of distant colonies arising either from tumour cells that disseminate during surgery or from undiagnosed micrometastases previously held in equilibrium before surgery. In this section, we describe and summarize the effect of perioperative factors on both the risk of local recurrence as well as the dissemination of cancer cells and their ability to form metastases (TABLE 1).

Intraoperative dissemination

Tumour cell dissemination can occur via the haematogenous, lymphatic, and/or transcoelomic (a route of tumour metastasis across a body cavity or organ surface including the pleural or peritoneal surfaces) routes. Circulating tumour cells (CTCs) are detectable in the majority of patients with solid tumours[30], and having an elevated number of CTCs has been linked with a poor prognosis in patients with various tumour

Table 1 | **Perioperative events postulated to influence the fate of residual cancer cells**

Physiological response to surgery	Perioperative triggers	Hypothesized effect
Increased circulating catecholamine levels	• Surgical tissue trauma • Anxiety • Pain • Hypothermia • Fasting	• Increased tumour-cell invasiveness • Increased transcription of metastasis-promoting factors • Formation of a pre-metastatic niche • Increased lymphatic flow and increased trafficking of cancer cells
Inflammation and wound healing	Surgical tissue trauma	• Provision of favourable growth conditions is amplified by influx of immune cells, fibroblasts, and mesenchymal stem cells to the wound • Wound hypoxia promotes malignancy and treatment resistance through hypoxia-inducible factor signalling • Endothelial glycocalyx effacement promotes interstitial tissue oedema, lymphatic flow, and cell trafficking • Systemic inflammation promotes the formation of a pre-metastatic niche
Immunosuppression	• Surgical tissue trauma • Hypothermia • Blood transfusion • Anaesthetic agents	• Inflammation and hypoxia subject tumour-associated immune cells to metabolic stresses, promoting M2-like macrophage activity and suppressing antitumour immune responses • Stress-induced repression of natural killer cell and $CD8^+$ T cell cytolytic capacity and trafficking diminishes the effectiveness of immune surveillance and termination of disseminated tumour cells • Shift to a T helper 2 cell phenotype and increased regulatory T cell numbers support evasion of the immune system by tumour cells
Platelet activation	Surgical tissue trauma	• Activated platelets shield CTCs from the effects of innate immunity • Formation of neutrophil extracellular traps and platelet–CTC aggregates assists the arrest of CTCs in distant organ capillary beds

CTC, circulating tumour cell.

types[31,32]. Notably, CTC numbers have been demonstrated to increase following surgery for breast[6], lung[7], and colorectal[8] cancers. Thus, while the evidence that high numbers of CTCs correlate with inferior patient outcomes across all tumour types is currently inconclusive[33], understandable concerns exist that tumour-cell release during surgery contributes to metastatic colonization.

Dissemination of tumour cells through lymphatic vessels occurs in response to surgical disruption and has been observed using real-time fluorescence imaging[34]. For example, an average fourfold increase in the number of DTCs following breast cancer surgery was detected in the sentinel lymph nodes of a cohort of 414 patients[35]. Preclinical research indicates that tumours have elevated levels of interstitial pressure that favours lymph flow to adjacent nodes and that this effect is enhanced by the normal mechanisms of lymphatic clearance of pericellular debris that follow wounding[36,37]. The inflammation and endothelial disruption resulting from surgical incision increase both hydrostatic and oncotic pressure levels in the interstitium, thereby leading to interstitial oedema, lymphatic transit of residual tumour cells, and their subsequent dissemination to distant sites[36,37]. This physiological response to wounding involves the upregulation of lymphangiogenic factors, including VEGF, prostaglandin, and PDGF, which might further increase both tumour cell dissemination and the viability of residual disease[38,39].

Transcoelomic dissemination of colorectal, pancreatic, or ovarian cancers during intra-abdominal surgery is a well-described phenomenon[17] that has also been shown to contribute to peritoneal carcinomatosis in mice[40]. This vulnerability to subsequent disease recurrence is highlighted by the finding that over a quarter of patients with colorectal cancer have detectable residual intra-abdominal cancer cells following surgery[41]. The intra-abdominal spread of tumours at the time of surgery might be further accelerated by the process of dehumidification, which occurs during carbon dioxide insufflation to facilitate laparoscopic surgery[40]. Dissemination of tumour cells might also be induced directly by the surgical procedure. For example, the use of laparoscopic ports can result in port-site recurrences: this phenomenon has been reported following surgery for gastrointestinal[42], gynaecological[43], urological[44], and thoracic[45] malignancies and, alarmingly, was reported to occur in >10% of patients following resection of incidentally diagnosed gall bladder cancer[46].

Wound healing after surgery

The processes of wound healing after surgery and tumour growth share common inflammatory processes, and a transcriptional 'wound response signature' not only resembles that of certain malignant cells but also has been associated with an inferior prognosis in patients with early stage breast cancer[47]. However, wound repair and cancer growth diverge fundamentally in the engagement of self-limiting mechanisms: in 1986, Harold Dvorak labelled tumours as "wounds that do not heal" (REF. 48).

Inflammatory changes that occur at the surgical site following tumour resection include the recruitment of numerous immune and/or inflammatory cell types and the release of humoral factors. Recruited macrophages and neutrophils, which secrete factors such as VEGF and matrix metalloproteinases (MMPs), are known to promote the growth and dissemination of cancer[49]. Similarly, tissue trauma leads to the recruitment of fibroblasts and mesenchymal stem cells to sites of endothelial

activation; these cells release soluble growth factors, thus providing the ideal conditions for the growth of residual cancer cells[50]. Surgery also increases the levels of circulating inflammatory mediators, such as prostaglandin E_2 (PGE_2)[51], which promotes an immunosuppressive tumour microenvironment through expansion of cancer-promoting regulatory T (T_{reg}) cells, reductions in the number of activated $CD8^+$ T cells, and a shift from the presence of predominantly antitumour T helper 1 (T_H1) cell cytokines towards tumour-promoting T_H2 cytokines[52,53]. Wounding during surgery might also disrupt the local vasculature, causing subsequent wound hypoperfusion, resulting in hypoxia and/or ischaemia[54]. Hypoxia stimulates the expression of hypoxia-inducible factors (HIFs)[55], which support cancer metabolism and drive tumour growth in a broad range of cancers[56].

Consistent with Paget's enduring 'seed and soil' model, a temporarily inflamed surgical wound might be an attractive site for colonization by CTCs. Inflammation denudes the microcirculatory endothelium, potentially creating a pre-metastatic niche. Notably, in animal models, injected cancer cells preferentially metastasize to regions of wounding created either by traumatic incisions or surgery-related inflammation[40,57,58], and research involving experimental models has shown that wound dehiscence is elevated in mice with disseminated tumours[59]. Dissemination to sites of inflammation might also explain the observed clinical phenomenon of cancer recurrence at the sites of a colonic anastomosis or abdominal port insertion[4,20,44,46].

The processes of a local inflammatory wound response and systemic inflammation together might activate dormant micrometastases or induce the propagation of residual cancer cells, thus increasing the risk of cancer recurrence. The findings of several *in vivo* studies demonstrate that wound-derived fluid, which is rich in PDGF, VEGF, and EGF, stimulates lymphangiogenesis and angiogenesis, leading to rapid neovascularization of dormant tumours[38,39,60,61]. Furthermore, in a zebrafish model of chronic wounding, leukocytes that migrate into a surgical wound have been shown to induce the proliferation of dormant tumour cells[62]. The degree of surgical stress and, therefore, the extent of the inflammatory response following surgery have been shown to correlate with the number of lung metastases observed in mouse models of metastatic cancer[63]. These observations are supported by the finding that patients undergoing surgery for non-small-cell lung cancer are more prone to cancer recurrence if they also have a high neutrophil-to-lymphocyte ratio[64]. The contribution of inflammatory wound repair processes to tumorigenesis might explain why surgical complications, including surgical wound infections (OR 2.87, 95% CI 1.97–4.18; $P < 0.0001$)[2], postoperative anastomotic leak (OR 1.61, 95% CI 1.25–2.09; $P < 0.05$)[4], and an increased perioperative systemic inflammatory response, are associated with an increased risk of cancer recurrence[65].

Activation of neural signalling

The surgical stress response is characterized by activation of the sympathetic nervous system, which is induced by tissue trauma during surgery as well as by patient anxiety, hypothermia, metabolic derangements, and fasting[66] (FIG. 1). Increased neural signalling results in the elevation of circulating adrenaline and noradrenaline levels, which act on both tumour cells and the tumour microenvironment through the activation of β-adrenoceptors to support the development of metastasis and cancer recurrence[67–70]. Consistent with this mechanism, evidence from *in vivo* cancer models has demonstrated that more-invasive surgery and higher levels of β-adrenoceptor activation are linked with increased tumour progression[15,63].

The findings of several studies show that activation of β-adrenoceptors promotes cancer progression in animal models of breast[67,68], pancreatic[69], colon[71], neuroblastoma[72], ovarian[70], and prostate cancers[73,74]. Other research has also shown that β-adrenoceptors are upregulated on tumour cells[75] and that activation of these receptors increases invasion and dissemination of tumour cells *in vivo*[76]. The signalling pathways that are stimulated by β-adrenoceptor activation in tumour cells include a cAMP signalling loop that upregulates the transcription of genes encoding metastasis-promoting factors, including HIFs, VEGF, and MMPs[67,69,77]. Activation of these signalling pathways results in structural changes in tumour cells that increase the formation of invadopodia (actin-rich protrusions from the plasma membrane that are associated with the formation of metastases)[78] and reduce the deformability of cells, resulting in contractile, invasive cells[77,79].

Neural signalling also remodels the architecture of the tumour microenvironment in a way that serves to accelerate cancer progression. Activation of β-adrenoceptor signalling promotes remodelling of the tumour-associated lymphatic and blood vasculature through inflammation-dependent mechanisms[67,68,70]. Furthermore, the sympathetic nervous system also regulates lymphatic flow through innervation of lymphangions, the structural contractile elements that surround lymphatic vessels and regulate the flow rate of lymphatic fluid[34,80,81]. Increased circulating catecholamine levels have been shown to accelerate flow through the lymphatic vessels that drain the primary tumour, thereby promoting the dissemination of tumour cells *in vivo*[68]. These findings raise the possibility that modulation of lymphatic flow during surgery might increase tumour cell dissemination. These effects might have important implications for the incidence of disease recurrence, given that patients undergoing more-invasive surgery generally have greater activation of neural signalling pathways[82] and that having an exaggerated perioperative neural-inflammatory response has been linked with inferior recurrence-free survival[65].

Catecholamine signalling through β-adrenoceptors might also increase the risk of cancer recurrence by creating an environment receptive to metastatic growth of DTCs. For example, stimulation of β_2-adrenoceptors on osteoblasts has been shown to upregulate Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL, also known as tumour necrosis factor ligand superfamily member 11), which increases osteoclast activity

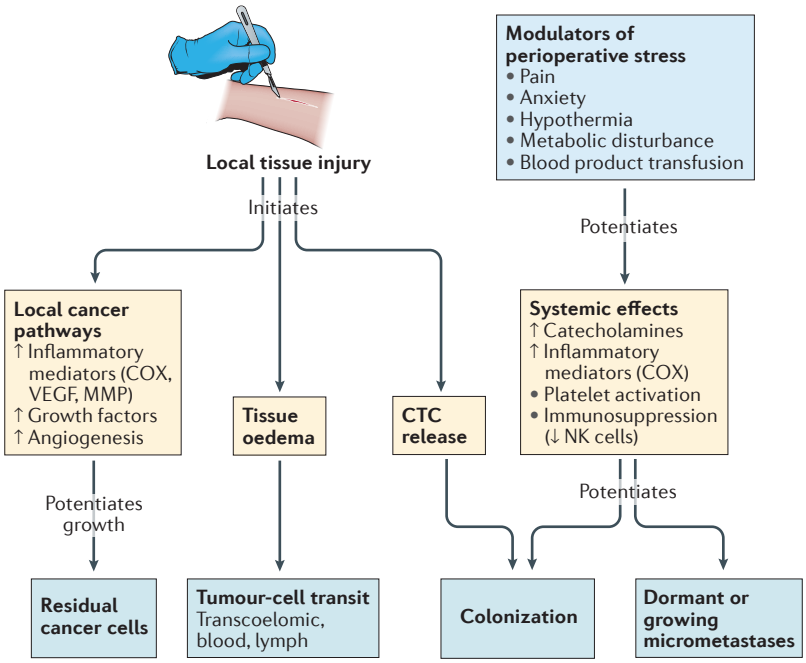

Figure 1 | **The effects of surgery and perioperative stress on cancer recurrence.** Tissue injury initiates inflammation and oedema at the wound site; these effects might promote the growth of residual tumour cells as well as tumour cell dissemination and distal colonization. Systemic effects of the perioperative stress response might also lead to the development of micrometastases as well as increase the vulnerability to cancer recurrence. COX, cyclooxygenase; CTC, circulating tumour cell; MMPs, matrix metalloproteinases; NK, natural killer.

and induces a bone microenvironment that supports metastasis[83,84]. Together, these observations suggest that elevated catecholamine levels in the perioperative period are an important factor that contributes to the growth of residual cancer cells (the 'seed') and might also assist in the establishment of distal sites of cancer deposition (the 'soil').

Surviving a hostile circulatory system

For tumour cells to survive in the circulation, they must be able to withstand exposure to shear stress and a lack of supporting extracellular matrix as well as be capable of evading detection by the immune system. For these reasons, few CTCs are thought to accomplish successful colonization of distal sites[85]. Nevertheless, injected cancer cells preferentially colonize areas of surgical inflammation[58], and in patients, CTCs are more likely to colonize wounds, infection sites, or areas of tissue trauma than uninjured tissue[2–4,57,86]. This observation raises the possibility that the risk of colonization is increased or at least that this process is more efficient during and/or immediately after surgery (FIG. 2). Therefore, an improved understanding of the mechanisms that support CTC survival in the perioperative setting might enable interventions that reduce the risk of successful colonization.

Following tissue damage during surgery, activation of platelets and tissue factors initiates coagulation in order to maintain haemostasis. However, this procoagulant and prothrombotic state might also confer vulnerability to malignant processes. Almost one-third of patients have thrombocytosis at the time of diagnosis with ovarian cancer[87], and the conclusions of a systematic review indicate that perioperative platelet elevation is associated with deleterious cancer outcomes[88]. Micro-clot formation and 'platelet cloaking' of liberated CTCs afford protection from both vascular shear stress[89] and detection by natural killer (NK) cells and facilitate microvascular arrest by promoting the attachment of CTCs to the endothelium[90]. By avoiding detection and elimination by marginalized leukocytes in the 'slow circulation points' of the pulmonary and hepatic capillaries, CTCs are able to survive extravasation and are able to establish metastases[91]. Inhibition of these platelet and clotting pathways (such as those involving tissue factor, thrombin, and/or von Willebrand factor) greatly reduces the incidence of metastasis in mouse models of cancer[92–94]. This effect is mediated by the activation of platelets and neutrophils, which triggers the formation of neutrophil extracellular traps (NETs) within sinusoids of the liver and lungs. NETs are created when activated neutrophils externalize their nuclear DNA, enabling them to form web-like structures. While these inflammatory adaptations might be advantageous to enable the entrapment of parasites and/or bacteria, NETs have also been shown to trap CTCs during cancer surgery, which has been shown to promote the formation of metastases in mouse models[95,96].

Following tissue injury, heparanase and hyaluronidase enzymes can affect CTC survival and colonization of distant tissues. Both enzymes are produced by cancer cells and are vital to the breakdown of the endothelial glycocalyx and thus facilitate the invasion and colonization of metastatic sites by CTCs[97,98]. The efficiency of colonization can be further improved by inflammatory mediators that aid in the destruction of the endothelial glycocalyx, with endothelial denudation resulting in the formation of a pre-metastatic niche[9]. This precursor state comprises clusters of bone-marrow-derived cells that populate and precondition the extracellular environment, enabling subsequent CTC infiltration and colony expansion[99]. Formation of the pre-metastatic niche might also be promoted by hypoxic conditions created at the site of surgical resection and by the actions of platelets, which release chemokines that attract bone-marrow-derived cells[10]. Therefore, perioperative strategies that prevent the development of conditions favouring the formation of a pre-metastatic niche, such as thrombi, NETs, and hypoxia, might reduce the risk of cancer recurrence after surgery.

Immune escape

Primary cancers and metastases use a range of strategies to evade detection and destruction by the immune system, many of which are activated in the aftermath of surgery. The localized inflammation, acidosis, and hypoxia that accompany tissue injury can also influence infiltrating immune cells, for example, by promoting the activity of pro-tumour M2-like macrophages and by suppressing antitumour immune responses[100]. Furthermore, under the influence of inflammatory mediators, such as PGE_2,

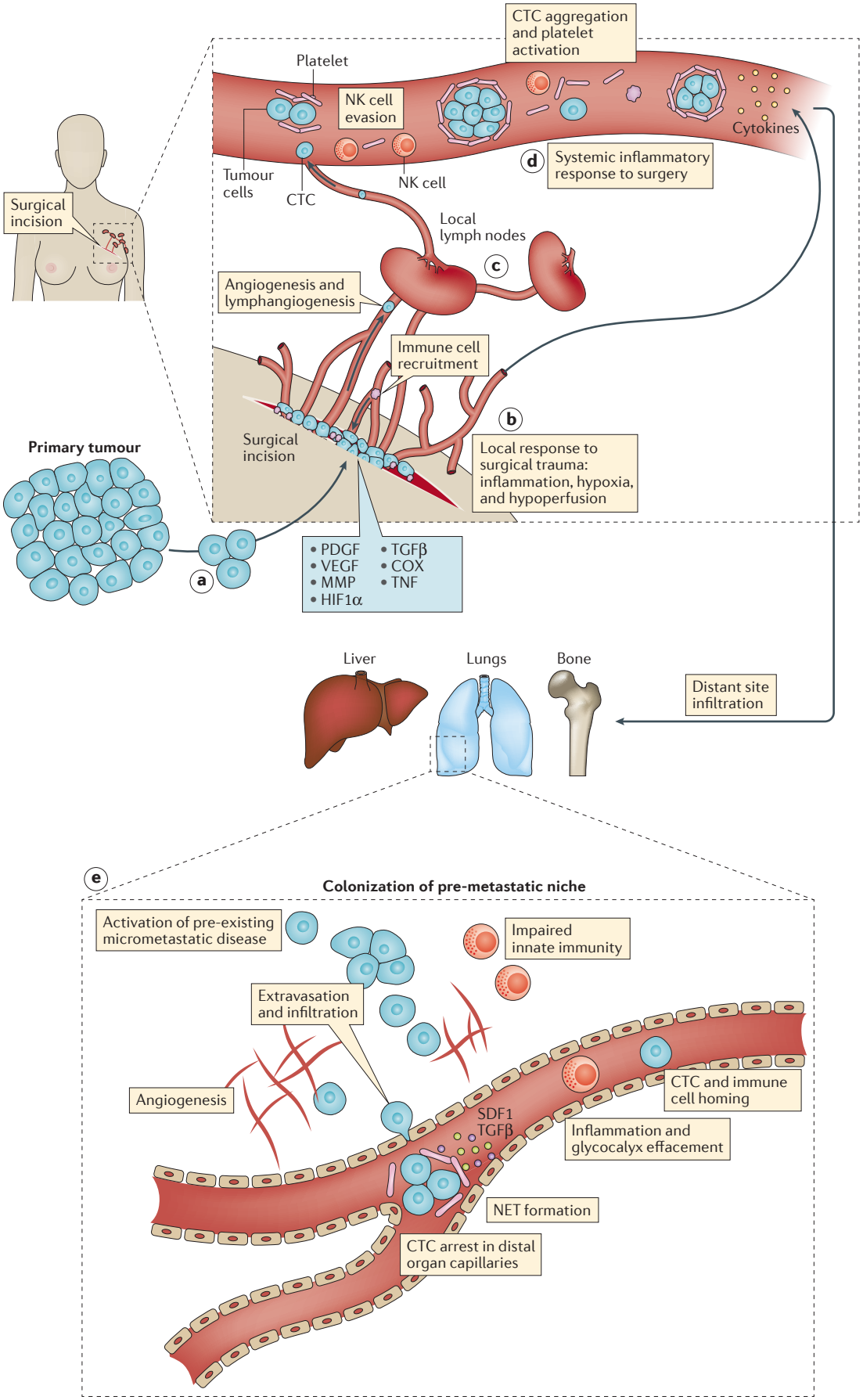

Figure 2 | **Putative mechanisms of postoperative cancer recurrence and metastasis.** **a** | A fraction of cancer cells might remain following tumour resection owing to incomplete resection margins, exfoliation into the surgical field, and distribution across major body cavities during surgery. **b** | Some of these cells disseminate via haematogenous and lymphatic routes, leading to spikes in circulating tumour cell (CTC) numbers in the days following surgery. Lymphatic trafficking accompanies the routine clearance of wound debris and is increased by elevated hydrostatic pressure following wound oedema and innervation of lymphangions by the sympathetic nervous system. **c** | The inflammatory response to surgical tissue trauma initiates the recruitment of bone-marrow-derived immune cells and endothelial cells and promotes the activation of fibroblasts, neovascularization, and the release of growth factors and cytokines. These conditions, which occur following wound hypoxia and the upregulation of hypoxia-inducible factor-1α (HIF1α), provide an ideal environment for the re-establishment of residual cancer cells. **d** | The surgical stress response induces inflammation, thrombocytosis, hypercoagulation, and impaired immunity. Perioperatively, CTCs have the potential to form aggregates and complexes with activated platelets, enabling them to withstand intravascular stresses and evade both circulating and specialized marginalized leukocytes. Platelets also release TGFβ and stromal-cell-derived factor 1 (SDF1), thus promoting CTC chemotaxis, and might initiate the transition of CTCs to a more-invasive, mesenchymal phenotype. **e** | The systemic inflammatory response to surgery aids the margination of CTCs in distant organ capillaries through endothelial activation, platelet interactions, formation of microthrombi, and the activation of neutrophil extracellular traps (NETs), which form a pre-metastatic niche. Surgical stress and exposure to general anaesthesia give rise to postoperative immunosuppression, providing CTCs with a privileged period with opportunities to colonize distant organs. COX, cyclooxygenase; MMP, matrix metalloproteinase; NK, natural killer; PG, prostaglandin.

tumour cells are able to shed cell-surface ligands in order to evade recognition by immune cells, including by NK cells[101]. Such effects reflect the temporary development of a tumour-promoting milieu in the surgical wound or at sites of micrometastases that might increase the risk of recurrence[4,20].

Following surgery, a protracted period of immunosuppression ensues. This counterbalancing phenomenon, sometimes referred to as the resolution phase of inflammation, has evolved to contain the intensity of acute inflammation but might also contribute to perioperative vulnerability to cancer recurrence. Activation of the hypothalamic–pituitary–adrenal axis by physical and psychological perioperative stressors results in the release of glucocorticoids, catecholamines, and cytokines that promote surgically induced immunosuppression[66,102]. The systemic immune consequences of these effects include diminished numbers and cytolytic capacity of NK cells and $CD8^+$ T cells and increased levels of tumour-promoting T_{reg} cells and T_H2 cells[11,12]. These changes have also been shown to increase the incidence of postoperative metastatic disease in animal models of cancer[103–105] and are associated with an increased risk of cancer recurrence and mortality in patients with a variety of tumour types[106]. Hence, minimizing surgical stress and therefore reducing the surgical stress response and limiting the subsequent immunosuppression to only that required for healing of the surgical wound might reduce a patient's vulnerability to cancer recurrence after surgery.

Reducing the risk of recurrence

The capacity of surgery-induced inflammation or elevation in circulating catecholamine levels to increase the proliferation of residual cells or DTCs suggests that the outcomes of patients with cancer can be improved by therapeutic strategies that aim to reduce the surgical stress response. This suggestion is timely: in 2015, an international onco-anaesthesia consensus panel prioritized the systematic investigation of perioperative factors that could potentially influence cancer recurrence[107]. Defining the full magnitude of effect of perioperative factors on long-term risk of cancer recurrence using well-designed, randomized, placebo-controlled prospective trials will be important. However, such trials will take a decade or more to recruit patients, monitor their outcomes, and report findings. Meanwhile, considerable evidence is currently available from preclinical and clinical studies indicating that agents with anti-adrenergic, anti-inflammatory, or antithrombotic properties, as well as the selection of specific anaesthesia techniques, might reduce a patient's risk of recurrence (TABLE 2). All these drugs are currently approved for clinical use, raising the possibility that their strategic use during the perioperative period of cancer resection surgery could reduce the risk of later disease recurrence and be readily implemented at minimal cost.

Inhibiting sympathetic signalling

Expanding evidence from both preclinical research[68] and retrospective studies[108,109] suggests that interventions specifically designed to modulate the sympathetic nervous system are an effective adjunctive strategy to reduce the risk of cancer recurrence. Perioperative inhibition of sympathetic signalling can be achieved pharmacologically using β-adrenoceptor antagonists (also known as β-blockers) or by neuraxial anaesthesia (in which an anaesthetic drug is administered near the nerves of the central nervous system to achieve blockade of sensory and sympathetic nerves). Several ongoing clinical trials are currently assessing the effects of perioperative β-blockers on oncological outcomes after surgery in patients with breast (NCT00502684, NCT01847001, NCT02596867), ovarian (NCT01308944, NCT01504126), or colorectal cancers (NCT00888797), or melanoma (NCT01988831). In other studies, the effects of perioperative neuraxial anaesthesia on cancer-specific outcomes are currently being investigated in patients with colorectal (NCT01318161, NCT02314871), breast (NCT00418457), or lung cancers (NCT02801409, NCT02840227) or melanoma (NCT01588847).

Coincidental use of β-blockers at the time of diagnosis is associated with improved oncological outcomes across patients with a broad range of tumour types, as reported following both retrospective studies[110] and prospective trials[111,112]. In particular, coincidental use of the β_1 and β_2 adrenoceptor-selective β-blocker propranolol is associated with improved survival outcomes in patients with breast cancer (HR 0.50, 95% CI 0.32–0.80)[113] and more specifically in those with early stage disease (HR 0.19, 95% CI 0.06–0.60)[108]. In preclinical studies, propranolol has been shown to inhibit a variety of β-adrenoceptor-mediated processes including tumour cell invasion[78], angiogenesis[70], lymphangiogenesis[68], and epithelial-to-mesenchymal transition[114]. Thus, propranolol could potentially be administered perioperatively

Table 2 | **Effects of anaesthetic agents and perioperative adjunctive therapies**

Perioperative intervention	Primary clinical use	Effects on tumour physiology and metastasis	Selected supporting clinical evidence
General anaesthetics	*Inhalational* Such as isoflurane, sevoflurane, desflurane for maintenance of anaesthesia	*Inhalational* Upregulation of HIF1α, VEGF, MMPs, and TGFβ; increased cellular migration, invasion, and immunosuppression	Single-centre retrospective analysis including data from 7,030 patients revealed an increased risk of death in patients receiving inhalational versus propofol-based intravenous anaesthesia (HR 1.46, 95% CI 1.29–1.66; $P<0.001$)[21]
	Intravenous Such as propofol; bolus administration for induction of anaesthesia and continuous infusion for maintenance	*Propofol* Known to have anti-inflammatory and anti-oxidant effects, inhibits cancer-cell migration while preserving T cell and NK cell function	
Neuraxial anaesthesia	• An alternative to general anaesthesia in patients undergoing lower body surgery • Provision of analgesic and anti-adrenergic effects when used as an adjunct to general anaesthesia	Suppression of circulating glucocorticoid and catecholamine levels in addition to those of several inflammatory mediators	• Meta-analysis of data from 51,620 patients revealed an association between use of neuraxial anaesthesia and overall survival (HR 0.85, 95% CI 0.74–0.98; $P<0.026$)[125] • Retrospective data are conflicting
β-blockers	• Inhibition of β-adrenoceptors to suppress the effects of elevated circulating catecholamine levels • Treatment of tachycardia, hypertension, and/or anxiety	• Inhibition of cancer cell invasion, lymphangiogenesis, angiogenesis, and recruitment of macrophages to the tumour • Reduction in lymphatic flow from tumours • Attenuation of deleterious effects of catecholamine signalling on antitumour immunity	Phase II trials evaluated the efficacy of perioperative propranolol during breast cancer surgery and found a reduction in metastasis transcriptional biomarkers[115] and modulation of immune cell number and function[12]
Cyclo-oxygenase inhibitors	• Inhibition of the synthesis of prostaglandins and other inflammatory mediators • Multimodal analgesia	• Inhibition of the development of a pro-inflammatory tumour microenvironment (through downregulation of VEGF, regulatory T cell infiltration): reduced angiogenesis and lymphangiogenesis • Reduction in NK cell suppression and metastasis in mouse models	• In cohort studies, NSAID use was associated with improved progression-free survival following surgery for breast cancer (HR 0.37, 95% CI 0.00–0.79; $P<0.019$)[137] or colorectal cancer (HR 0.20, 95% CI 0.07–0.60)[138] • Retrospective analysis including data from 15,574 patients undergoing liver resection revealed an association between postoperative NSAID use and risk of disease recurrence (HR 0.81, 95% CI 0.73–0.90; $P<0.001$)[139]
Antithrombotics	• Venous thromboembolism prophylaxis (heparin) • Perioperative aspirin use is balanced between improved cardiovascular outcomes and increased risks of perioperative haemorrhage	• Heparin inhibits heparanase-mediated CTC–platelet complex formation, attachment to endothelial glycocalyx, and metastasis • In addition to inhibition of prostaglandin synthesis, aspirin possibly also impairs platelet-mediated CTC survival	• Cohort studies found that perioperative use of aspirin is associated with improved outcomes in patients with breast, colorectal, gastric, or biliary cancers[166] • In a randomized controlled trial, 5-year survival of patients randomized to receive aspirin following oesophagectomy was 51.2%, compared with 41.0% in the placebo group; $P=0.04$)[167]

CI, confidence interval; CTC, circulating tumour cell; HIF1α, hypoxia-inducible factor 1α; HR, hazard ratio; MMP, matrix metalloproteinases; NK, natural killer.

to inhibit the brief period of surgery-induced activation of the sympathetic nervous system and thereby reduce the risk of cancer recurrence. This approach has been successfully demonstrated in *in vivo* studies involving rat or mouse models, in which brief, clinically relevant dosing of propranolol (for example, as would occur before surgery) reduced the extent of tumour cell proliferation, lymph drainage, and metastatic colonization[68,104].

Two randomized double-blind clinical trials completed in the past 2 years have promoted the translation of these preclinical findings to the clinical setting. In one trial, women were prescribed either the combination of propranolol (40 mg daily) plus the NSAID etodolac (800 mg daily) or placebo for 5 days before breast cancer surgery and for 5 days after surgery[115]. The investigators found that drug treatment, compared with placebo, partially mitigated the postoperative increase in inflammation as indicated by serum IL-6 levels (4.4-fold versus 5.7-fold increase, respectively; $P<0.001$) and serum C-reactive protein levels (6.3-fold versus 8.3-fold increase, respectively; $P<0.001$), both of which are markers of the severity of the surgical stress response. Propranolol plus etodolac, compared with placebo, also prevented the preoperative increase in inflammatory marker levels (IL-6, 11% versus 24%, $P<0.0009$; C-reactive protein, 10% versus 41%, $P<0.034$), suggesting that preoperative anxiety primes patients' stress responses before surgery. Notably, drug treatment also

reduced the expression of several tumour-promoting genes including transcription factors involved in the promotion of metastasis, recruitment of myeloid cell types, and epithelial-to-mesenchymal transition. These findings demonstrate that brief inhibition of perioperative neural or pro-inflammatory signalling reduces the malignant potential of tumour cells at the time of surgery. Defining the relative contributions of β-blockers and NSAIDs to these effects will be important. A separate trial[12] examined the effect of propranolol (60 mg daily) on postoperative peripheral immune cell numbers. Treatment with propranolol was commenced on the day of mastectomy and was found to mitigate against postoperative elevation of circulating T_{reg} cell numbers and suppression of a tumour-antigen-specific $CD4^+$ T cell response.

These findings raise the possibility that perioperative modulation of neural signalling or inflammation might offset surgery-related immunosuppression and reduce the malignant potential of residual cancer cells. However, trials involving large cohorts of patients have shown that clinicians must be cautious with the prescription of β_1-adrenoceptor-selective β-blockers in patients with a high risk of cardiovascular adverse events[116], especially when administered at a high dose in the immediate preoperative period. Propranolol might be more suitable for perioperative use because it is not β_1-adrenoceptor-selective and is already occasionally used as a preoperative anxiolytic[117]; the perioperative safety of this agent has been demonstrated in two prospective trials[12,115].

Neuraxial anaesthesia, used in addition or as an alternative to general anaesthesia, reduces circulating catecholamine levels, inflammation, immunosuppression, and provides an alternative means of achieving sympathetic blockade during cancer surgery[82], inflammation, and immunosuppression[118–120]. Furthermore, the findings of a study published in 2016 indicate that perioperative lymph flow is inhibited by use of neuraxial anaesthesia[81], a phenomenon that has also been documented in animal models[121]. This observation raises the intriguing possibility that a potential anticancer effect of neuraxial anaesthesia might result from a reduction in the extent of dissemination of residual cancer cells from a surgical wound. As a commonly used perioperative analgesic technique, neuraxial anaesthesia enables clinicians to implement opioid-sparing perioperative pain relief[109,122]. This approach is thought to be advantageous during cancer surgery owing to *in vivo* evidence of tumour-promoting effects of opioids in mouse models[123]. However, avoidance of perioperative use of opioids when attempting an opioid-free anaesthetic procedure clearly should not be undertaken if it creates a risk of poorly managed perioperative pain and thus activation of the sympathetic nervous system[124]. Overall, the conclusions of two meta-analyses of predominantly retrospective data published in the past 3 years show that the use of perioperative neuraxial anaesthesia is associated with a survival benefit (HR 0.85, 95% CI 0.74–0.98; $P = 0.026$ (REF. 125); HR 0.84, 95% CI 0.75–0.94 (REF. 126)). Neuraxial anaesthesia is already in routine use during cancer surgery as an analgesic technique for lower limb or major abdominal–pelvic surgery. Determining whether neuraxial anaesthesia or perioperative use of β-blockers provides oncological benefits to patients will require evidence from the aforementioned ongoing randomized trials, which aim to reduce the risk of recurrence and to improve long-term outcomes.

Anti-inflammatory therapy

NSAIDs are commonly used as analgesics in the perioperative setting and might also provide additional anticancer benefits. NSAIDs are either non-selective (for example, aspirin, diclofenac, naproxen, ibuprofen, and ketorolac) or selective for either the constitutively expressed cyclooxygenase 1 (COX1) isoform (ketoprofen) or the inducible COX2 isoform (celecoxib, parecoxib, etodolac, and rofecoxib). Several clinical trials designed to investigate the effects of routine perioperative use of NSAIDs on reducing the risk of cancer recurrence are currently ongoing: two trials are currently at the follow-up monitoring stage (NCT01806259, NCT02429427), and two trials are actively recruiting patients undergoing surgery for either breast (NCT00502684) or colon (NCT00888797) cancer.

NSAIDs inhibit tumour-associated inflammation, and in animal models of cancer have been shown to reduce the extent of angiogenesis and lymphangiogenesis and to inhibit the development of metastasis[68,127]. The use of NSAIDs during surgery has been shown to reduce the level of inflammation, with suppression of NK cell numbers, and to prevent the formation of metastases in mouse models of cancer[103,105].

The findings of various clinical studies also suggest that NSAIDs have both localized and systemic anti-inflammatory effects. Trials with results published in the past 5 years have shown that perioperatively administered COX2 inhibitors reduce prostaglandin levels both in the circulation and at the surgical site[128,129], suppress circulating catecholamine and cytokine levels[128,130], and buffer both the elevation of T_{reg} cell numbers[131] and the decline in NK cell counts following surgery[132]. NSAIDs also have an established chemopreventive effect on the formation of a variety of tumour types[133,134], and preoperative use of these agents has been shown to reduce intratumoural levels of VEGF expression, lymphangiogenesis, and T_{reg} cell infiltration[135,136]. Data from these clinical studies point to an indirect anticancer effect. Nevertheless, in several studies, investigators have reported an association between perioperative use of NSAIDs and improved outcomes of patients with cancer[137–139]. The largest of these studies involved a cohort of 15,574 patients undergoing liver resection for hepatocellular carcinoma and revealed an association between perioperative administration of NSAIDs and a reduced risk of cancer recurrence (HR 0.81, 95% CI 0.73–0.90; $P < 0.001$)[139]. COX2 inhibitors have been recommended, over other NSAIDs, to provide postoperative analgesia following cancer surgery[122].

Anaesthetic drugs

As early as the 1980s, experimental research demonstrated that anaesthetic drugs influence both cancer cell proliferation and metastasis[140]. Evidence from studies with outcomes reported in the past 5 years suggests that the two most common anaesthetic agents — intravenous propofol and inhalational volatile anaesthetics — have distinct influences on inflammation, immune cell phenotypes, and cancer progression. Given that nearly 80% of the 15 million patients diagnosed annually with cancer will require anaesthesia, improving our understanding of the divergent effects of these agents on cancer biology will guide the choice of the most-appropriate anaesthetic for cancer surgery[24].

Inhalational anaesthetics. Inhalational halogenated hydrocarbon anaesthetics, including isoflurane and sevoflurane, are known to afford a degree of cytoprotection to organs including the heart, brain, and kidneys and to reduce both infarct size and functional impairment in models of ischaemia–reperfusion injury[141]. These properties, however, might make such agents deleterious when used in patients with cancer. For example, the cytoprotective effects of inhalational anaesthetics have been linked to HIF1α upregulation and could therefore confer a survival benefit on residual cancer cells[142]. This hypothesis is supported by the findings of several *in vitro* studies in which exposure to even brief periods of isoflurane caused the upregulation of HIF1α, HIF2α (also known as EPAS1), and TGFβ and increased the transcription of genes encoding several metastasis-promoting factors (VEGF, angiopoietin 1, MMP2, and MMP9)[143,144] that increase tumour cell proliferation and migration[145–147]. Data from *in vivo* studies demonstrate that isoflurane modulates T_H1:T_H2 ratios[148], impairs NK cell activity[149], and increases the migration of cancer cells[150]. Inhalational anaesthetic agents might thus promote immunosuppression and the development of a pro-malignant environment that supports the growth of residual cancer cells. Taken together with the available clinical data, the currently routine use of inhalational anaesthetics for cancer surgery is now being questioned and evaluated against the possible use of potentially safer alternatives, such as intravenous anaesthesia. This concern achieved further clinical relevance with the publication of data from a retrospective, propensity-matched cohort of >7,000 patients with cancer. The authors found that use of volatile anaesthesia is associated with a remarkable reduction in long-term overall survival outcomes after cancer surgery compared with propofol-based anaesthesia (22.8% versus 15.6% mortality at 5 years after surgery; HR 1.46, 95% CI 1.29–1.66; $P < 0.001$), even after controlling for comorbidity risk and the presence of metastatic disease at surgery[21]. This finding is particularly alarming given that volatile anaesthesia is used in up to 90% of general anaesthetic procedures[151]. Thus, prospective multicentre studies involving large cohorts of patients are warranted in order to address the effect of volatile anaesthesia during cancer surgery on cancer recurrence.

Propofol. Intravenous propofol provides an alternative to inhalational anaesthesia and is already in common use for cancer surgery. Propofol has appealing anticancer properties, and the past 3 years have seen a rapid expansion in the number of prospective trials evaluating the effects of propofol (compared with volatile anaesthetic agents) on the outcomes of patients with cancer, including its effects on immune or cancer-specific biomarkers (NCT03005860, NCT02739958, and NCT01418326) or on mortality in phase IV studies (NCT01975064, NCT03034096, NCT02660411, NCT02840227, and ACTRN12617001065381).

The association between propofol and improved patient survival following cancer surgery[21,22] might reflect the anti-inflammatory properties of this agent. Propofol has been shown to suppress prostaglandin and inflammatory cytokine production in mouse models of cancer[152–154]. Administration of propofol has also been shown to reduce cytokine production[155] and prevent immunosuppression[156]. Data from *in vitro* and *in vivo* experiments have shown that clinically relevant concentrations of propofol or exposure to serum from patients who were anaesthetized using propofol inhibits cancer cell migration via suppression of MMP expression, preserves NK cell function, and reduces the formation of metastases[157–160]. Increased infiltration of tumours with NK cells is also reported in patients who were anaesthetized using propofol[149]. These findings suggest that propofol has advantageous anti-inflammatory effects during cancer surgery that could confer long-term improvements in patient outcomes. Consistent with this suggestion, the findings of a retrospective study demonstrate that, in patients undergoing mastectomy, use of propofol anaesthesia is associated with improved survival compared with use of volatile anaesthesia (HR 0.55, 95% CI 0.31–0.97)[161]. More research is required, although current evidence raises the possibility that total intravenous anaesthesia with propofol could soon become the standard anaesthetic agent for all cancer surgery.

Antithrombotics

Antithrombotic agents, such as aspirin and heparin, are routinely used during the perioperative period to reduce the risk of myocardial infarction, cerebrovascular thrombosis, and venous clot formation. By inhibiting platelets from the cloaking effects of CTCs, these agents reduce metastatic colonization[162,163]. Several clinical trials designed to investigate the influence of perioperative antithrombotics on the long-term outcomes of patients undergoing surgery for breast (NCT02927249) or colon cancer (NCT02301286, NCT02467582) are currently ongoing.

In addition to established anti-inflammatory effects, aspirin also has antithrombotic effects via inhibition of thromboxane A_2; these effects might partially explain why aspirin is the only NSAID reported to reduce the incidence of cancer[164]. A reduced risk of metastasis has also been reported in patients receiving aspirin and might be attributable to impaired CTC survival, owing to the antiplatelet properties of aspirin[165].

Data from two studies demonstrate that daily aspirin use following cancer surgery is associated with a reduced risk of metastasis (OR 0.48, 95% CI 0.30–0.75; $P < 0.0001$) and a reduced risk of cancer-related death in colorectal cancer (OR 0.61, 95% CI 0.55–0.67; $P < 0.0001$), with similar associations seen in patients with oesophageal, breast, gastric, or biliary cancers[166,167]. Furthermore, in a prospective observational study involving patients with rectal cancer, investigators found that patients receiving concurrent low-dose aspirin in combination with neoadjuvant chemotherapy had a favourable pathological response, a lower risk of metastasis (HR 0.30, 95% CI 0.10–0.86; $P = 0.05$), and improved 5-year progression-free survival (HR 0.20, 95% CI 0.07–0.60)[138]. Perioperative activation of COX enzymes, with CTC release during surgical manipulation and a consequent increase in risk of colonization, represents a cancer-promoting vulnerability associated with the perioperative period that seems to be partially offset by use of low-dose aspirin. Use of aspirin should be avoided in patients with cardiovascular risk factors and an increased risk of postoperative bleeding[168]. Guidelines published in 2016 suggest that aspirin can be safely incorporated into perioperative treatment regimens designed to reduce the risk of metastasis and cancer mortality[169].

Alternative antithrombotic agents to aspirin, such as heparin, have also been shown to prevent or delay cancer progression in both *in vitro* and *in vivo* studies[170]. Heparin inhibits heparanase enzymes, thus reducing the risk of primary tumour angiogenesis and disease progression and increasing the rate of tumour cell apoptosis[171,172]. Similar to aspirin, heparin inhibits the formation of platelet–CTC complexes[173] and inhibits the development of metastases in experimental models[172,174]. Notably, the β-blocker propranolol can also inhibit thromboxane synthesis and reduce platelet aggregation, which might contribute to the anti-metastatic properties of propranolol[175]. However, whether or not antithrombotic agents, such as aspirin, enable the achievement of a beneficial anticancer effect through inhibition of CTC survival requires further investigation. The increasing abundance of preclinical evidence supporting the use of this strategy does build a case for the perioperative use of such agents in patients with a low risk of bleeding complications.

Translating research into clinical practice

Worldwide, more than nine million patients with cancer require surgery each year. These patients will be exposed to various pathophysiological stresses during the perioperative period and will undergo various different types of anaesthesia. Accumulating evidence suggests that these factors can promote the survival of residual cells or DTCs and initiate cancer recurrence. Thus, understanding how perioperative care should be adapted to reduce the risk of localized or metastatic recurrence is currently a leading research priority[24,107]. Notably, the current paucity of robust evidence has resulted in a lack of consensus on the optimal approach to perioperative care, and no guidelines currently exist on the optimal anaesthetic technique during cancer surgery.

The current body of evidence suggests that optimal care during cancer surgery will involve the use of anti-adrenergic, anti-inflammatory, and/or antithrombotic strategies underpinned by the use of neuraxial anaesthesia and total intravenous anaesthesia, which has the potential to improve long-term survival outcomes. The findings of several ongoing clinical trials are expected to provide greater levels of insight into the potential anticancer benefits of such strategies. The utility of this anaesthetic strategy could be especially applicable to certain patient subgroups, including those with an existing preoperative inflammatory state, those with a high CTC load, and those with an elevated perioperative risk of infectious or anastomotic complications[2,4,65,88,176].

Conclusions

Many novel cancer therapies cost thousands of US dollars per patient and might not dramatically improve patient outcomes[177]; however, many of the perioperative interventions highlighted in this Review can be costed in single-dollar figures per patient. Large-cohort prospective clinical trials are required to definitively demonstrate the effects of different anaesthetic techniques on long-term outcomes after cancer surgery. Should the findings of the retrospective studies described in this Review be prospectively confirmed, considerable global economic and social improvements in the outcomes of patients with cancer can be achieved at relatively little financial cost but with potentially life-changing benefits that will bring about a paradigm shift in surgical cancer care.

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Review criteria
A broad literature search was conducted using the PubMed and Google Scholar databases. Principal search terms included 'surgery', 'anaesthesia', 'cancer recurrence', 'metastasis', 'immunosuppression', 'circulating tumour cells', and 'inflammation'. Results were confined to published full-text articles written in English. No constraints were placed upon year of publication. The reference lists of selected publications identified through the initial search were subsequently used to identify further leads.