Perioperative events influence cancer recurrence risk after surgery

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Abstract

Surgery is a mainstay of treatment for solid tumours. Despite surgical resection with curative intent and advances in (neo)adjuvant therapies, metastatic disease remains common and carries high mortality. The biological perturbation that accompanies the surgical stress response and the pharmacological effects of anaesthetic drugs may paradoxically promote progression of metastatic disease. When cancer cells persist after surgery either locally or at undiagnosed distant sites, neuroendocrine, immune, and metabolic pathways, which are activated in response to surgery and anaesthesia, may promote their survival and proliferation. The consequence is that minimal residual disease may escape equilibrium and progress to metastatic disease. Here, we discuss leading proposals for refinement of perioperative care that address these challenges. We outline the rationale and early evidence for the adaptation of anaesthetic techniques and strategic use of anti-adrenergic, anti-inflammatory, and anti-thrombotic therapies. Many of these strategies are now under evaluation in major cancer surgery trials and hold promise as affordable, readily available measures to improve post-operative recurrence-free survival.

Introduction

Surgery is the foremost treatment strategy for the majority of solid tumours. However, even where complete loco-regional control is thought to have been achieved, post-operative recurrence is common and carries high mortality[1]. The stress response to surgery activates physiological responses that have evolved to promote wound healing after injury. These include neural, inflammatory, and pro-angiogenic signalling pathways, which also promote cancer growth and metastasis. Unsurprisingly, accumulating evidence suggests that perioperative events promote recurrence by enhancing growth of pre-existing micrometastatic disease or by facilitating a residual fraction of tumour cells to develop loco-regional recurrence or seed new metastatic disease[2-4].

Over a century ago, Paget proposed a 'Seed and Soil' framework that described metastasis in terms of cancer cell dissemination and colonization in 'fertile soil'[5]. Such an analogy is highly relevant to the perioperative period, when both cancer cell dissemination and perturbations in tissue environments occur. Handling of the tumour during surgery can release cancer cells into circulation (the seed)[6-8]. Meanwhile, vulnerability to colonization arises from the modulation of immune function and the activation of neural-inflammatory signalling, which may prime local and distant tissue beds to form a privileged microenvironment (the pre-metastatic niche, or soil)[9,10]. This period of vulnerability may extend in excess of a week after surgery and help the 'seed' to 'germinate and fertilize' and thereby establish viable minimal residual disease[11,12]. As a consequence, local cancer recurrence or metastasis development following surgery has been documented in numerous tumour types including breast[13,14], ovarian[15], lung[16], and colorectal cancers[17].

Clinical findings suggest that the magnitude of surgery and protracted inflammation caused by post-operative complications may further increase the risk of disease recurrence. For example, compared with a simple mastectomy, an additional invasive reconstructive procedure alters cancer recurrence dynamics[18,19]. Additionally, post-operative complications such as wound infection[2,3] or anastomotic leak[4,20] have been associated with poor cancer-related outcomes. Alarmingly, recent clinical studies raise the possibility that the choice of anaesthetic agent may also impact long-term survival in patients with cancer[21,22]. This emphasizes the patient vulnerability to recurrence that arises from exposure to perioperative events.

The potential magnitude of impact of this perioperative vulnerability is underscored by the fact that more than 60% of the over 15 million patients diagnosed with cancer each year will require surgical resection[23], and that more than 80% of cancer patients will be exposed to anaesthesia for either curative, diagnostic or palliative procedures[24]. As such, any opportunity to abrogate cancer risk arising during the vulnerable perioperative period may lead to substantial benefit for patients globally. Here, we review the biological processes that underpin this vulnerability to cancer recurrence, as well as the accumulating pre-clinical and clinical evidence that anaesthetic and adjunctive strategies may modulate the risk of cancer recurrence following surgery.

Pathophysiological response to surgery

Post-operative recurrence frequently takes the form of metastatic disease[13,14]. The traditional paradigm sees metastasis as a late event in the stepwise, Darwinian-like evolution of cancers, occurring only when cells acquire a complementary set of somatic genetic changes that allow escape from the primary tumour, entry into the lymphatic or vascular network, circulatory survival, and an ability to establish growth at ectopic sites[25]. The "parallel progression" model challenges this perspective, unifying a series of clinical and experimental observations that collectively suggest that dissemination and distant colonization occur early in the development of a cancer[26]. Early support for this came from genetic analyses of patients with breast cancer, where disseminated tumour cells isolated from bone marrow displayed fewer genetic aberrations than their matched primary tumour counterparts[27]. More recently, the phenomenon has been captured and mechanistically characterized in animal models of pancreatic cancer[28] and breast cancer[29], in which epithelial-mesenchymal transition programmes promoted the dissemination and distant colonization of early cancer cells even before primary tumours had become detectible. In the perioperative context, these findings suggest that cells liberated during surgery, even when originating from very early-stage tumours, may be competent to disseminate and form metastases.

Moreover, it is increasingly evident that the fate of disseminated tumour cells may be determined by the conditions encountered during transit and the early stages of colonization. Events during intravascular passage, such as interactions with activated platelets, neutrophils, and endothelial cells, as well as transient exposure to pro-metastatic, pro-angiogenic signals that accompany the surgical inflammatory response may improve metastatic efficiency[25]. Given that the pathophysiological response to surgery bears many similarities with conditions that are favourable for cancer progression, it follows that events in the perioperative period could influence the viability and subsequent expansion of distant colonies arising either from tumour cells disseminated during surgery, or from undiagnosed micrometastatic sites that were held in equilibrium prior to surgery. Here, we review the events of cancer cell dissemination and colonization that are impressionable to perioperative factors (summarized in Table 1).

Intra-operative tumour cell dissemination

Tumour cell dissemination occurs via haematogenous, lymphatic, and transcoelomic routes. Circulating tumour cells (CTCs) are detectable in the majority of patients with solid tumours[30], and elevated CTC levels have been linked to poor prognosis in various tumour types[31,32]. CTC numbers have been demonstrated to rise following surgery for breast[6], lung[7], and colorectal[8] cancers. While there is inconclusive evidence that CTC elevation correlates with poor outcomes in all tumour groups[33], it understandably raises concern that CTC release during surgery contributes to metastatic colonization.

Dissemination of tumour cells through lymphatic vasculature occurs in response to mechanical (surgical) disruption and has been captured using real-time fluorescence imaging[34]. A four-fold increase in tumour cells was detected in sentinel lymph nodes following breast cancer surgery[35]. Tumours have an elevated interstitial pressure that favours lymph flow to adjacent lymph nodes and this is enhanced by the normal

mechanisms of lymphatic clearance of pericellular debris that follow wounding[36,37]. The inflammatory-mediated endothelial disruption resulting from surgical incision elevates both the hydrostatic and oncotic pressures in the interstitium, thereby leading to interstitial oedema, lymphatic transit of residual tumour cells and subsequent dissemination[36,37]. This physiological response to wounding, with up-regulation of lymphangiogenic factors including vascular endothelial growth factor (VEGF), prostaglandins, and platelet derived growth factor (PDGF), may further enhance tumour cell dissemination and viability of residual disease[38,39].

Transcoelomic dissemination of colorectal, pancreatic or ovarian cancers during intra-abdominal surgery is a well-described phenomenon[17] and contributes to peritoneal carcinomatosis[40]. This vulnerability for subsequent recurrence is highlighted by the finding that up to one quarter of patients had detectible residual intra-abdominal cancer cells following colorectal surgery[41]. Intra-abdominal spread of tumours at the time of surgery may be further accelerated by the process of dehumidification, which occurs during gas (carbon dioxide) insufflation to facilitate laparoscopic surgery[40]. Dissemination of tumour cells may also be induced directly by the surgical procedure, for example the use of laparoscopic ports may result in port site recurrence. This phenomenon has been reported following surgery for gastrointestinal[42], gynaecological[43], urological[44], and thoracic[45] malignancies, and alarmingly was recently reported to be over 10% following gall-bladder resection where incidental malignancy was diagnosed[46].

Inflammation and wound healing after surgery

Wound healing following surgery and tumour growth share common inflammatory processes, and a transcriptional 'wound response signature' resembles that expressed by malignant cells[47]. However, where wound repair and cancer growth fundamentally diverge is in the employment of self-limiting mechanisms; Dvorak labelled tumours as "wounds that do not heal"[48].

Inflammatory changes that occur at the surgical site following cancer resection include recruitment of numerous cell types and release of humoral factors. Recruited macrophages and neutrophils, which secrete factors such as VEGF and matrix metalloproteinases (MMP), are known to promote cancer growth and dissemination[49]. Similarly, tissue trauma recruits fibroblasts and mesenchymal stem cells to sites of endothelial activation; these cells release soluble growth factors to form ideal growth conditions for residual cancer cells[50]. Surgery elevates inflammatory mediators such as prostaglandin E_2 (PGE_2)[51], which promotes an immunosuppressive environment through expansion of cancer-promoting regulatory T cells (T_{reg}), reduction of CD8+ T cells, and a shift from anti-tumour Th1 to Th2 cytokines[52,53]. Surgical wounding also disrupts local vasculature, causing subsequent wound hypoperfusion (ischaemia) and hypoxia[54]. Hypoxia stimulates expression of hypoxia-inducible factor (HIF)[55], which supports cancer metabolism to drive tumour growth in a broad range of cancers[56].

Consistent with Paget's enduring 'seed and soil' model, an inflamed surgical wound temporarily may 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 (traumatic incision) or surgically related inflammation[40,57,58] and experimental models have shown that wound dehiscence is elevated in mice with disseminated tumours[59]. Tumour cell dissemination to sites of inflammation may

explain the observed clinical phenomena of cancer recurrence at the site of a colonic anastomosis or abdominal port insertion[4,20,44,46].

Together, the processes of a local inflammatory wound response and systemic inflammation may activate dormant micrometastasis or propagate residual cancer cells to increase the risk of cancer recurrence. *In vivo* studies found that wound derived fluid, which is rich in PDGF, VEGF, and epidermal growth factor, stimulates lymphangiogenesis and angiogenesis leading to rapid neovascularization of dormant tumours (micrometastasis)[38,39,60,61]. Leukocytes that migrate into a surgical wound have been shown to induce proliferation of dormant tumour cells[62]. Increased inflammatory response following surgery correlates with increased metastasis development in animal models[63], and patients with a high neutrophil to lymphocyte ratio are more prone to cancer recurrence[64]. The contribution of inflammatory wound repair processes to tumourigenesis may explain why surgical complications including surgical wound infections (Odds Ratio [OR] 2.87, 95% Confidence Interval [CI]: 1.97-4.18)[2], post-operative anastomotic leak (OR 1.61, 95% CI: 1.25-2.09)[4], and increased perioperative systemic inflammatory response are associated with elevated cancer recurrence[65].

Activation of neural signalling

The surgical stress response is characterized by activation of neural signalling, which is induced by surgical tissue trauma as well as the pathophysiological stress effects of patient anxiety, hypothermia, metabolic derangements, and fasting (Figure 1)[66]. Increased neural signalling elevates circulating catecholamine levels that act through β-adrenoceptors to induce pro-metastatic effects on both tumour cells and the tumour microenvironment to support cancer recurrence[67-70]. Consistent with this, *in vivo* cancer models have demonstrated that more invasive surgery and high levels of neural-inflammatory signalling are linked with increased tumour progression[15,63].

In vivo studies show that neural signalling through β-adrenoceptors enhances cancer progression in models of breast[67,68], pancreas[69], colon[71], neuroblastoma[72], ovarian[70], and prostate cancers[73,74]. Studies have shown that β-adrenoceptors are up-regulated on tumour cells[75], and activation increases invasion and dissemination *in vivo*[76]. The signalling pathways that are activated in tumour cells by β-adrenoceptor stimulation include a calcium-cAMP signalling loop that enhances transcription of pro-metastatic factors including HIF, VEGF, and MMP[67,69,77]. Activation of these signalling pathways results in structural changes in tumour cells that increase formation of invadopodia[78] and reduce cell deformability resulting in contractile, invasive cells[77,79].

Neural signalling also remodels the architecture of the tumour microenvironment to accelerate cancer progression. β-adrenoceptor signalling remodels tumour-associated lymphatic and blood vasculature through inflammation-dependent mechanisms[67,68,70]. The sympathetic nervous system also regulates lymphatic flow through innervation of lymphangions – structural contractile elements that surround lymphatic vessels and regulate pumping[34,80,81]. A recent study found that neural signalling accelerates flow through lymphatic vessels that drain the primary tumour, thereby increasing dissemination of tumour cells *in vivo*[68]. These findings raise the possibility that modulation of lymphatic flow during surgery may enhance tumour cell dissemination. This may have significant implications for recurrence incidence, as activation of neural pathways is elevated in more invasive surgery[82], and an exaggerated

perioperative neural-inflammatory response has been linked to poor cancer-free survival[65].

Neural signalling may also enhance recurrence by creating a metastatic microenvironment that promotes growth of disseminated tumour cells. Stimulation of β_2-adrenoceptors on osteoblasts up-regulates the Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), which increases osteoclast activity and induces a microenvironment in the bone that supports expansion of metastasis[83,84]. Together these observations suggest that elevated neural signalling in the perioperative period is an important factor that may contribute to the growth of residual cancer cells (seed) and may assist the establishment of distal sites of cancer deposition (soil).

Surviving a hostile circulatory system

For tumour cells to survive in circulation they must withstand shear forces, a lack of supporting extracellular matrix, as well as evade detection by circulating immune defences. For these reasons, few CTCs are thought to accomplish colonization of distal sites[85]. Nevertheless, injected cancer cells preferentially colonize areas of surgical inflammation[58] and in patients, CTCs home to wounds, infection sites or areas of tissue trauma[2-4,57,86]. This raises the possibility that colonization is enhanced, or at least is more efficient during and after surgery (Figure 2). Understanding the mechanisms that support CTC survival in the perioperative setting may lead to interventions that reduce the odds of successful colonization.

Following surgical injury, activation of platelets and tissue factor initiates coagulation to achieve haemostasis. However this pro-coagulant and pro-thrombotic state may confer vulnerability to malignant processes. Almost a third of patients have thrombocytosis at the time of ovarian carcinoma diagnosis[87], and a recent systematic review found perioperative platelet elevation associates with deleterious cancer outcomes[88]. Micro-clot formation and 'platelet cloaking' of liberated CTCs affords protection from vascular shear stress[89], natural killer (NK) cell-mediated detection, and facilitates microvascular arrest by promoting CTC attachment to the endothelium[90]. By avoiding detection and elimination by marginated leukocytes in the 'slow circulation points' of the pulmonary and hepatic capillaries, CTCs are able to survive extravasation and establish metastases[91]. Inhibition of these platelet and clotting pathways (tissue factor, thrombin, von Willebrand factor) greatly reduces metastasis in mouse models of cancer[92-94]. Activation of platelets and neutrophils 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 to form web-like structures. While these inflammatory adaptations may be advantageous to trap parasites and bacteria, NETs have also been shown to trap CTCs during cancer surgery[95,96].

Following tissue injury, CTC survival and colonization is also influenced by production of the enzymes heparanase and hyaluronidase. Both enzymes are produced by cancer cells and are vital to the process of endothelial glycocalyx breakdown that facilitates the adhesion (colonization) and invasion of CTCs at metastatic sites[97,98]. The efficiency of colonization may be further improved by inflammatory mediators that aid the destruction of the endothelial glycocalyx, with endothelial denudation forming a pre-metastatic niche[9]. This comprizes clusters of bone-marrow derived cells that populate and pre-condition an environment for subsequent CTC infiltration and

colony expansion[99]. Pre-metastatic niche formation may also be enhanced by hypoxic conditions created at the site of surgical resection and by the actions of platelets that release chemokines that are attractive to bone-marrow derived cells[10]. Therefore, perioperative strategies that prevent conditions that favour the formation of a pre-metastatic niche (such as thromboses, NETs, and hypoxia) may reduce recurrence after surgery.

Immune escape

Primary cancers and metastases employ a range of strategies to evade immune detection, many of which are enhanced in the inflammatory aftermath of surgery. The inflammation, acidosis, and hypoxia that accompany local tissue injury influence infiltrating immune cells, for example promoting M2 macrophage activity and suppressing anti-tumour immune responses[100]. Furthermore, under the influence of inflammatory mediators such as PGE_2, tumour cells shed surface ligands to prevent recognition by immune cells, including NK cells[101]. Such effects can hence lead to a temporary pro-cancer milieu in the surgical wound or at sites of micrometastasis that may increase the risk of recurrence[4,20].

Following surgery, a protracted period of immunosuppression ensues: a counterbalancing phenomenon that has evolved to contain the intensity of the acute inflammation, but may also contribute to the perioperative vulnerability to cancer recurrence. Activation of the hypothalamic-pituitary-adrenal axis by physical and psychological perioperative stressors results in release of glucocorticoids, catecholamines, and cytokines that promote surgically-induced immunosuppression[66,102]. The systemic immune consequences of these effects include diminished number and cytolytic capacity of NK and CD8+ T cells, and increased pro-tumour T_{reg} and Th2 cell levels[11,12]. These changes have been shown to increase post-operative metastatic disease in animal models of cancer[103-105], and are associated with increased risk of cancer recurrence and mortality in a variety of tumour types in patients[106]. Hence, minimizing the surgical stress response and limiting the subsequent immunosuppression to that required for healing the surgical wound might be a strategy to reduce the vulnerability to cancer recurrence following surgery.

Reducing vulnerability to cancer recurrence

The capacity of surgery-induced neural-inflammatory signalling to enhance growth of residual or disseminated tumour cells suggests that it may be possible to improve cancer survival by emphasizing therapeutic strategies that reduce the surgical stress response. This is timely, as a recent international oncoanaesthesia consensus panel prioritized systematic investigation of perioperative factors that potentially influence cancer recurrence[107]. It will be important to define the magnitude of effect of perioperative factors on long-term cancer recurrence through randomized, placebo-controlled prospective trials. However, these will take a decade or more to recruit, monitor outcomes, and report findings. Meanwhile, there is considerable evidence available from pre-clinical and clinical studies that agents with anti-adrenergic, anti-inflammatory, or anti-thrombotic properties, as well as specific anaesthesia techniques, may have anti-cancer benefits (Table 2). As these drugs are already approved for use in the perioperative period, these findings raise the possibility that

their strategic use during cancer resection surgery could reduce opportunity for later recurrence and be readily implemented with minimal cost.

Blockade of sympathetic nervous system signalling

Expanding evidence from pre-clinical research[68] and retrospective studies[108,109] suggest that blockade of peripheral sympathetic nervous system (SNS) signalling may be an effective adjunctive anti-oncogenic strategy. Perioperative SNS blockade may be achieved pharmacologically by β-adrenoceptor antagonism or by the delivery of neuraxial anaesthesia. Several prospective trials are currently assessing the role of perioperative beta-blocker treatment on improved cancer outcomes after surgery in patients with breast (NCT00502684, NCT01847001, NCT02596867), melanoma (NCT01988831), and colorectal (NCT00888797) cancer. Further studies are investigating the impact of perioperative neuraxial anaesthesia on cancer-specific outcomes in colorectal (NCT00684229, NCT0131861, NCT02314871), melanoma (NCT01588847), breast (NCT00418457), and lung (NCT02801409, NCT02840227) cancer.

For patients with cancer, co-incidental beta-blocker use at the time of diagnosis is associated with oncological benefit across a broad range of tumours as reported in both retrospective studies[110] and prospective trials[111,112]. In particular, the non-selective beta-blocker propranolol is associated with improved survival in breast cancer (Hazard Ratio [HR] 0.50, 95% CI: 0.32-0.80)[113], specifically in early stage disease (HR 0.19, 95% CI: 0.06-0.60)[108]. Propranolol inhibits a variety of β-adrenoceptor-mediated cancer processes including tumour cell invasion[78], angiogenesis[70], lymphangiogenesis[68], and epithelial-mesenchymal transition[114]. Propranolol administration is thus a strategy that could be used perioperatively to inhibit the brief period of surgery-induced neural activation and its adverse effects on cancer processes. This has been successfully demonstrated *in vivo* where brief, clinically-relevant dosing of propranolol (for example, as would occur prior to surgery) reduced tumour cell proliferation, lymph drainage, and metastatic colonization by tumour cells[68,104].

Two recently completed randomized double-blind clinical trials have translated these pre-clinical findings to the cancer surgical setting. In one surgical trial, women were prescribed either the non-selective β-adrenoceptor antagonist propranolol (40 mg daily) combined with the anti-inflammatory etodolac (800 mg daily), or placebo, for five days prior to breast cancer surgery[115]. The investigators found that drug treatment (compared with placebo) buffered the surgical stress response, as indicated by reduced serum inflammatory markers at the time of surgery (interleukin-6, C-reactive protein). Treatment also buffered an increase in serum inflammatory markers from pre-treatment until the day of surgery, suggesting pre-operative anxiety may prime patients' stress response prior to surgical injury. Notably, drug treatment also reduced tumour gene expression signatures that were characteristic of pro-metastatic transcription factors, myeloid recruitment, and epithelial-mesenchymal transition. These findings demonstrate that brief blockade of perioperative neural-inflammatory signalling downgrades the malignant potential of tumour cells at the time of surgery. It will be important to define the relative contributions of beta-blockade and NSAIDs to these effects. A separate surgical trial examined the effect of propranolol (60 mg daily) on post-operative immune cell changes[12]. Beta-blocker treatment that was commenced on the day of mastectomy surgery mitigated post-operative elevation of

T_{reg} cells and suppression of tumour antigen-specific CD4 T cell response.

These findings raise the possibility that perioperative modulation of neural-inflammatory signalling may offset surgery-related immunosuppression and potentially reduce the malignant potential of residual cancer cells. Large trials have shown that clinicians must be cautious with prescription of cardio-selective beta-blockers in patients at risk of cardiac events[116], especially when administered in a high dose in the immediate preoperative period. However, propranolol may be more suitable for use in the perioperative oncoanaesthesia context as it is not cardio-selective, is used as a pre-operative anxiolytic[117], and has now demonstrated safety in two prospective cancer trials[12,115].

An alternate means of achieving sympathetic blockade during cancer surgery is through neuraxial anaesthesia that reduces circulating catecholamines[82], inflammation, and immunosuppression[118-120]. Furthermore, a recent study reports that perioperative lymph flow is inhibited by neuraxial anaesthesia[81], a phenomenon also documented in animals[121]. This raises the intriguing possibility that a potential 'anti-cancer' benefit from neuraxial anaesthesia may result from a reduction in dissemination of residual cancer cells from a surgical wound. As a commonly used perioperative analgesic technique, neuraxial anaesthesia allows clinicians to implement opioid-sparing perioperative care[109,122]. This approach is thought to be advantageous during cancer surgery due to *in vivo* evidence of tumour promoting effects by opioids[123]. What is clear is that avoidance of perioperative opioids when endeavouring an opioid-free anaesthetic should not be undertaken if it risks poorly managed perioperative pain and thus sympathetic activation[124]. Overall, recent meta-analyses show that perioperative neuraxial anaesthesia is associated with a survival benefit (HR 0.85, 95% CI: 0.74-0.98)[125], HR 0.84, 95% CI: 0.75-0.94[126]). Neuraxial anaesthesia is already in routine use during cancer surgery when indicated. Whether it or perioperative beta-blockade provide cancer-specific benefit for patients will require evidence from the randomized trials listed above that target long-term recurrence outcomes.

Anti-inflammatory therapy

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in the perioperative setting as analgesics and may also have additional anti-cancer benefit. NSAIDs are non-selective (aspirin, diclofenac, naproxen, ibuprofen, ketorolac) or selective for either the constitutive cyclo-oxygenase (COX)-1 isoform (ketoprofen) or inducible COX-2 isoform (celecoxib, parecoxib, etodolac, rofecoxib). Several clinical trials are currently investigating the impact of routine perioperative NSAIDs on reducing cancer recurrence: two are currently closed for follow-up (NCT01806259, NCT02429427), and two are actively recruiting in breast (NCT00502684) and colon (NCT00888797) cancer surgery.

NSAIDs inhibit tumour-associated inflammation, which reduces angiogenesis and lymphangiogenesis to block metastasis in animal models of cancer[68,127]. This suggests that perioperative NSAID use may limit surgically-induced inflammatory states. Consistent with this, use of NSAIDs during surgery reduced inflammation and NK cell suppression, and prevented metastasis in mouse models of cancer[103,105].

Clinical studies also suggest that NSAIDs exert localized and systemic anti-inflammatory and immune effects. Recent surgical trials have shown perioperative administered COX-2 inhibitors reduce systemic and wound prostaglandin levels[128,129], suppress catecholamine and cytokine levels[128,130], and buffer both T_{reg} elevation[131] and NK cell decline[132]. NSAIDs have an established chemoprevention role in a variety of tumour types[133,134], and their pre-operative use reduces intra-tumoural VEGF expression, lymphangiogenesis, and T_{reg} infiltration[135,136]. While these clinical studies point to an indirect anti-cancer benefit, several studies have also reported an association between use of perioperative NSAIDs and improved cancer outcomes for patients[137-139]. The largest of these studies investigated 15,574 patients receiving liver resection for hepatocellular carcinoma and found an association between perioperative administration of NSAIDs and reduced cancer recurrence (HR 0.81, 95% CI: 0.73-0.90)[139]. COX-2 inhibitors have been recommended over other NSAIDs for post-operative analgesia during cancer surgery[122].

Anaesthetic drugs

As early as the 1980s, experimental research demonstrated that anaesthetic drugs influence cancer cell proliferation and metastasis[140]. Recent evidence suggests that the two most common anaesthesia agents – intravenous propofol and inhalational volatile – have distinct influences on inflammation, immune cell phenotypes and cancer processes. Given that nearly 80% of the 15 million new patients diagnosed annually with cancer will require anaesthetic agent exposure, improving our understanding of the divergent impact of these agents on cancer biology will guide appropriate anaesthetic choice for cancer surgery[24].

Inhalational anaesthetics

Inhalational halogenated hydrocarbon anaesthetics including isoflurane and sevoflurane are well known to afford a degree of cytoprotection to organs such as the heart, brain, and kidneys, and reduce both infarct size and functional impairment in models of ischemia-reperfusion injury[141]. However, these properties may make them deleterious in the cancer setting. Their cytoprotective effects have been linked to HIF-1α up-regulation, and could confer a survival benefit on residual cancer cells[142]. This hypothesis is supported by recent *in vitro* studies, where exposure to even brief periods of isoflurane led cancer cells to up-regulate HIF-1α, HIF-2α, and transforming growth factor-β, and increase transcription of pro-metastatic factors (VEGF, angiopoietin-1, proteases MMP-2 and MMP-9)[143,144] which enhanced tumour cell proliferation and migration[145-147]. *In vivo* studies show that isoflurane modulates Th1:Th2 ratios[148], impairs NK cell activity[149], and enhances the migration of cancer cells[150]. Inhalational anaesthetic agents may thus promote immunosuppression and a pro-malignant environment that supports growth of residual cancer cells. Taken together with the available clinical data, the currently routine practice of using inhalational anaesthetics for cancer surgery is being questioned and evaluated against potentially safer alternatives. This concern achieved further clinical relevance with the recent publication of a retrospective, propensity matched cohort of over 7000 cancer patients that found use of volatile anaesthesia was associated with a remarkable reduction in long-term overall survival after cancer surgery when compared with propofol based anaesthesia (22.8% versus 15.6% mortality five years after surgery; HR 1.46, 95% CI: 1.29-1.66), even after controlling for patient comorbid risk and for metastatic disease at surgery[21]. This is particularly alarming as volatile anaesthesia is used in up to 90% of general anaesthetic procedures[151]. Large, prospective multi-

centre studies are warranted to address the safety of volatile anaesthesia during cancer surgery.

Propofol

The alternative anaesthesia agent in common use during cancer surgery is intravenous propofol. Propofol has an appealing anti-cancer profile, and the last three years have seen a rapid expansion in the number of prospective trials evaluating its impact during cancer surgery (compared with volatile anaesthetic agents) on immune or cancer-specific biomarkers (NCT03005860, NCT02739958, NCT01418326) or in phase four (mortality) studies (NCT01975064, NCT03034096, NCT02660411, NCT02840227, ACTRN12617001065381).

The association between propofol and improved patient survival following cancer surgery[21,22] may be linked to its anti-inflammatory properties. Propofol suppresses prostaglandin and inflammatory cytokine production in mouse models of cancer[152-154]. In patients, perioperative propofol reduces cytokine production[155] and prevents immunosuppression[156]. *In vitro* and *in vivo* experiments have shown that clinically relevant concentrations of propofol, or serum from patients who were anaesthetized with propofol, inhibit cancer cell migration via inhibition of MMP expression, preserve NK cell function, and reduce metastasis[157-160]. Increased NK cell infiltration of tumours is also reported in patients administered propofol[149]. These findings suggest that propofol may provide anti-inflammatory advantages during cancer surgery that could confer long-term benefit on cancer outcome. Consistent with this, a recently published retrospective study found that in patients undergoing mastectomy, propofol anaesthesia was associated with improved survival compared with volatile anaesthesia (HR: 0.55, 95% CI: 0.31-0.97)[161]. While more research is required, current evidence raises the possibility that total intravenous anaesthesia with propofol may become the preferential anaesthetic agent for cancer surgery.

Anti–thrombotics

Anti-thrombotic agents such as aspirin and heparin are used during the perioperative period to reduce the risk of myocardial infarction, cerebrovascular thrombosis, and venous clot formation. By inhibiting platelet cloaking of CTCs, these agents may prevent metastatic colonization[162,163]. Several clinical trials are currently investigating the influence of perioperative anti-thrombotics on long-term cancer outcomes following breast (NCT02927249) and colon cancer surgery (NCT02301286, NCT02467582).

In addition to its anti-inflammatory effects, aspirin exerts an anti-thrombotic effect via inhibition of thromboxane A_2; this may partially explain why aspirin is the only NSAID to reduce the incidence of cancer[164]. It has been proposed that reduced metastasis in patients receiving aspirin is attributable to impairment of CTC survival by the anti-platelet properties of aspirin[165]. Studies have found that daily aspirin use following colorectal surgery is associated with reduced metastasis (OR 0·69, 95% CI: 0·57-0·83) and improved survival (OR 0.62, 95% CI: 0.58-0.67), with similar associations seen in oesophageal, breast, gastric, and biliary cancers[166,167]. Furthermore, a recently published prospective observational study of patients with rectal cancer found those taking low-dose aspirin concurrently with neoadjuvant chemotherapy had a favourable pathological response, lower metastasis risk (HR 0.30, 95% CI: 0.10-0.86), and improved five year progression-free survival (HR 0.20,

95% CI: 0.07-0.60)[138]. Perioperative COX activation with CTC release during surgical manipulation, and consequent colonization risk represents a cancer promoting vulnerability associated with the perioperative period that appears to be partially offset by low dose aspirin. While aspirin should be avoided in high risk patients[168], especially with increased bleeding risk, recent guidelines suggest that aspirin may be safely incorporated into perioperative treatment to reduce the risk of metastasis and cancer mortality[169].

Alternative anti-thrombotic agents such as heparin have also been shown to prevent cancer progression in *in vitro* and *in vivo* studies[170]. Heparin inhibits heparanase to reduce primary tumour angiogenesis, increase apoptosis, and reduce tumour progression[171,172]. Like aspirin, heparin inhibits platelet-CTC complexes[173], and prevents metastasis in experimental models[172,174]. Notably, the beta-blocker propranolol may also inhibit thromboxane to reduce platelet aggregation, which may contribute to its anti-metastatic properties[175]. Whether anti-thrombotic agents such as aspirin achieve a beneficial anti-cancer effect through inhibition of CTC survival requires further study. However, the increasing evidence supporting this strategy builds a case for their perioperative use in patients at low risk of bleeding complications.

Translating research: improving clinical practice

More than nine million cancer patients worldwide require cancer surgery each year. These patients will be exposed to the pathophysiological stresses of the perioperative period and to various anaesthetic techniques. Accumulating evidence points to these factors potentially promoting the survival of residual or disseminated cancer cells to initiate cancer recurrence. Understanding how perioperative care should be adapted to reduce the risk of local or metastatic recurrence is a leading research priority[24,107]. Notably, the paucity of robust evidence has resulted in a lack of consensus on optimal perioperative care, and no guidelines exist for the choice of anaesthetic technique during cancer surgery.

The existing body of evidence suggests that optimal care during cancer surgery will employ an anti-adrenergic, anti-inflammatory, anti-thrombotic strategy underpinned by the use of neuraxial anaesthesia and total intravenous anaesthesia, and may improve long-term survival. On-going clinical trials will provide greater insight into the potential anti-cancer benefit of such strategies. The utility of this anaesthetic technique may be especially applicable in certain patient sub-groups including those with an existing preoperative inflammatory state, those with high CTC load and those at an elevated perioperative risk of infectious or anastomotic complications[2,4,65,88,176].

While many novel oncological therapies are costed in thousands of dollars per patient, the perioperative interventions highlighted in this review can be costed in single dollar figures per patient. Large prospective clinical trials are required to definitively demonstrate the effect of anaesthetic techniques on long-term outcomes after cancer surgery. Should this be confirmed, then significant global economic and social improvements in cancer outcomes can be achieved for patients at relatively little financial cost but with potentially life-changing benefit that will bring about a paradigm shift in surgical cancer care.

Glossary

General anaesthesia agent: A drug used to induce and maintain a state of general anaesthesia. Broadly categorized as inhaled (e.g., sevoflurane, isoflurane, desflurane) or intravenous (e.g., propofol, thiopentone).

Iatrogenic: Relating to illness or injury caused by medical examination or treatment.

Neuraxial anaesthesia: An anaesthetic drug placed near the nerves of the central nervous system to achieve blockade of sensory and sympathetic nerves. This is commonly achieved by subarachnoid or epidural injection.

Transcoelomic: A route of tumour metastasis across a body cavity or organ surface including the pleural or peritoneal surfaces.

Key points

- While surgery remains the primary treatment for solid tumours, post-operative loco-regional recurrence and metastasis occurs frequently and confers a high morbidity and mortality.
- Deleterious aspects of surgery include initiation of local and systemic inflammation, a pro-thrombotic state, exposure to anaesthetic drugs, immunosuppression, and neural activation of adrenergic signalling. These processes overlap with known cancer promoting pathways.
- During surgery, cancer cells that escape resection are subject to perioperative physiological changes, and may disseminate and colonize distant organs, contributing to post-operative cancer recurrence.
- Perioperative use of anti-adrenergic drugs, anti-inflammatories, intravenous anaesthesia agents, and anti-thrombotic agents are linked with improved cancer survival.
- Over 60% of patients with cancer are treated with surgery. Off-setting the deleterious impact of surgery using affordable and readily available therapies may help to rapidly improve post-operative cancer survival.

Acknowledgements

This work was supported by the Australian and New Zealand College of Anaesthetists, The David and Lorelle Skewes Foundation, the Peter Mac Foundation, and the National Cancer Institute (CA160890).

Contributions

J.G.H, N.J.P, B.R, and E.K.S researched data for the article. All authors wrote, reviewed and edited the manuscript before submission. J.G.H and N.J.P contributed equally.

Competing Interests

The authors declare no competing interests

Author Biographies

J.G.H is a clinical and research anaesthetist at the Peter MacCallum Cancer Centre whose research programme focuses on translational studies of perioperative adjunctive therapies applicable to the care of patients undergoing cancer surgery. His research explores anti-inflammatory and stress minimization strategies that lead to

enhanced recovery and improved long-term cancer outcomes for patients. He is a PhD student at Monash University, Australia.

N.J.P is an anaesthetic trainee in the Imperial School of Anaesthesia and a Cancer Research UK Clinical Research Fellow at the Institute of Cancer Research. He is studying the effects of general anaesthetic drugs on cancer cell biology to determine their potential contribution to post-operative cancer outcomes. He received his MBBS and BSc degrees from Imperial College London, where he first began his research into this topic in the lab of Daqing Ma.

G.P leads the Signalling and Cancer Metabolism Team at the Institute of Cancer Research and is an Honorary Senior Lecturer at Imperial College London. He received his PhD from the University of Cambridge and carried out post-doctoral training at Harvard Medical School with Lew Cantley. Ongoing projects in his group examine the role of PTEN-PI3K/Akt/mTOR pathway in metabolic rewiring with the view to discover how the interplay between tumour and adjacent stroma may provide opportunities for novel cancer treatments.

B.R has clinical, educational, and research interests in the field of oncoanaesthesia. He promotes a global collaborative effort to further understand the impact of the perioperative adrenergic-inflammatory response and anaesthetic technique on tumor-progression signaling as strategies to improve long-term outcomes following cancer surgery.

E.K.S. is a cancer biologist who studies neural regulation of the tumour microenvironment. Her research team discovered that external stressors act through the sympathetic nervous system to promote metastasis by modulating the behaviour of both tumour cells and the tumour microenvironment. These findings have identified multiple targets to slow cancer progression that are under clinical evaluation.

Review Criteria

A broad literature search was conducted using the PubMed database and Google Scholar. 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 for further leads.

Tables

Table 1. Perioperative events postulated to influence the fate of residual cancer cells and post-operative disease recurrence

Physiological response to surgery	Perioperative triggers	Hypothesized impact upon tumour cells and metastasis
Sympathetic nervous system activation	Surgical tissue trauma Anxiety Pain Hypothermia Fasting	Increased tumour cell invasiveness Increased transcription of pro-metastatic factors Formation of 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 tumour malignancy and treatment resistance through HIF Endothelial glycocalyx effacement promotes interstitial tissue oedema, lymphatic flow, and cell trafficking Systemic inflammation promotes formation of a pre-metastatic niche
Immunosuppression	Surgical tissue trauma Hypothermia Blood transfusion Anaesthetic agents	Inflammation and hypoxia subjects tumour-associated immune cells to metabolic stresses, promoting M2-like macrophage activity and suppression of anti-tumour immune responses Stress-induced repression of NK and CD8+ cell cytolytic capacity and trafficking diminishes efficacy of immune surveillance and killing mechanisms against disseminated tumour cells Shift to Th2 cell phenotype and increased T_{reg} numbers supports immunoevasion by tumour cells
Platelet activation	Surgical tissue trauma	Activated platelets shield CTCs from innate immune defence mechanisms NET formation and platelet-CTC aggregates assist CTC arrest in distant organ capillary beds

HIF, Hypoxia-Inducible Factor; NK, natural killer; T_{reg}, regulatory T cell; CTC, circulating tumour cell; NET, neutrophil extracellular trap

Table 2. Anaesthetic agents and perioperative adjunctive therapies and their potential impact upon cancer cells, metastasis, and cancer outcomes

Perioperative Intervention	Primary clinical use	Impact on tumour physiology and metastasis	Selected supporting clinical evidence
General anaesthetics	● *Inhalational* e.g. isoflurane, sevoflurane, desflurane for maintenance of anaesthesia ● *Intravenous* e.g. propofol; bolus administration for induction of anaesthesia and continuous infusion for maintenance	● *Inhalational agents*: Up-regulate HIF-1α, VEGF, MMP, TGF-β Increase cell migration, invasion Immunosuppression ● *Propofol:* Anti-inflammatory, anti-oxidant Inhibits cancer cell migration Preserves T and NK cell function	● Single-centre retrospective analysis of 7,030 patients found a HR 1.46 (95% CI: 1.29-1.66) for death in patients receiving inhalational versus propofol based anaesthesia[21]
Beta-blockers	● Antagonism of β-adrenergic receptors to inhibit response to endogenous catecholamines ● Treat tachycardia, hypertension, anxiety	● Inhibit cancer cell invasion, lymphangiogenesis, angiogenesis, and recruitment of macrophages to the tumour ● Reduce lymphatic flow from tumours ● Attenuate deleterious effects of catecholamine signalling on anti-tumour immunity	Phase II trial of perioperative propranolol in breast cancer found beta-blockade reduced EMT, pro-metastatic transcription, and immunosuppression (T_{reg}, $CD4^+$ T cell)[12,115]
Neuraxial anaesthesia	● Used as an alternative to general anaesthesia for lower-body surgery ● Analgesic & anti-adrenergic adjunct to general anaesthesia	● Suppresses glucocorticoids, catecholamines, and inflammatory mediators	● Meta-analysis reports an association between neuraxial anaesthesia and overall survival HR 0.85 (95% CI: 0.74-0.98)[125] ● Conflicting retrospective data
Cyclooxygenase inhibitors	● Anti-inflammatory action to reduce prostaglandin production ● Used for multi-modal analgesia	● Inhibit a pro-inflammatory tumour microenvironment (VEGF, T_{reg} infiltration): reduce angiogenesis and lymphangiogenesis ● Reduce NK cell suppression and metastasis in mouse models	● Retrospective analysis of 15,574 patients undergoing liver resection reports an association between NSAIDs and reduced recurrence (HR 0.81, 95% CI: 0.73-0.90)[139] ● NSAID use associated with improved outcomes for colorectal and breast cancer surgery[137,138]
Anti-thrombotics	● Heparin used for veno-thromboembolism prophylaxis ● Perioperative aspirin use is balanced between cardiovascular advantages and risks of perioperative haemorrhage	● Heparin inhibits heparanase-mediated CTC-platelet formation, attachment to endothelial glycocalyx, and metastasis ● Additional to its anti-prostaglandin effects, aspirin possibly impairs platelet-mediated CTC survival	● Perioperative aspirin associated with improved outcome in breast, oesophageal, colorectal, gastric, and biliary cancers [166,167]

HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinases; TGF-β, transforming growth factor; NK, natural killer; HR, hazard ratio; CI, confidence interval; EMT, epithelial mesenchymal transition; T_{reg}, regulatory T cell; NSAID, non-steroidal anti-inflammatory drug; CTC, circulating tumour cell

Figure Legends

Figure 1 **| The impact of surgery and perioperative stress on the processes of cancer recurrence**
Local tissue injury initiates inflammation and oedema at the wound site, though these effects may also facilitate growth of residual tumour cells as well as tumour cell dissemination and distal colonization. Systemic effects of the perioperative stress response may activate micrometastasis as well as enhancing the vulnerability to recurrence. COX, cyclooxygenase; VEGF, vascular endothelial growth factor; MMPs, matrix metalloproteinases; CTC, circulating tumour cell; NK, natural killer cell.

Figure 2 **| Putative mechanisms for post-operative cancer recurrence and metastasis**
A| Following tumour resection, a fraction of cancer cells remain due to incomplete resection margins, exfoliation into the surgical field, and distribution across major body cavities during tumour handling. **B|** Some of these cells disseminate via haematogenous and lymphatic routes, leading to spikes in circulating tumour cells (CTCs) in the days following surgery. Lymphatic trafficking accompanies normal clearance of wound debris and is enhanced by raised hydrostatic pressure from wound oedema and innervation of lymphangions by the sympathetic nervous system. **C|** The inflammatory response to surgical tissue trauma initiates recruitment of bone marrow-derived immune cells, endothelial cells and fibroblast activation, neovascularization, and release of growth factors and cytokines. These conditions, occurring with wound hypoxia and the up-regulation of hypoxia inducible factor (HIF)-1α, 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 may form aggregates and complexes with activated platelets to help withstand intravascular stresses and evade both circulating and specialized marginated leukocytes. Platelets also release transforming growth factor (TGF)-β and stromal-derived factor (SDF)-1 to promote CTC chemotaxis and may initiate transition of CTCs to a more invasive, mesenchymal phenotype. **E|** The systemic inflammatory response to surgery aids CTC margination in distant organ capillaries through endothelial activation, platelet interactions, micro-thrombus formation, and neutrophil extracellular traps (NETs) which form a pre-metastatic niche. Surgical stress and exposure to general anaesthesia give rise to post-operative immunosuppression, providing CTCs a privileged period for colonization. COX-2, cyclooxygenase-2; PGE_2, prostaglandin-E_2; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

Figure 1

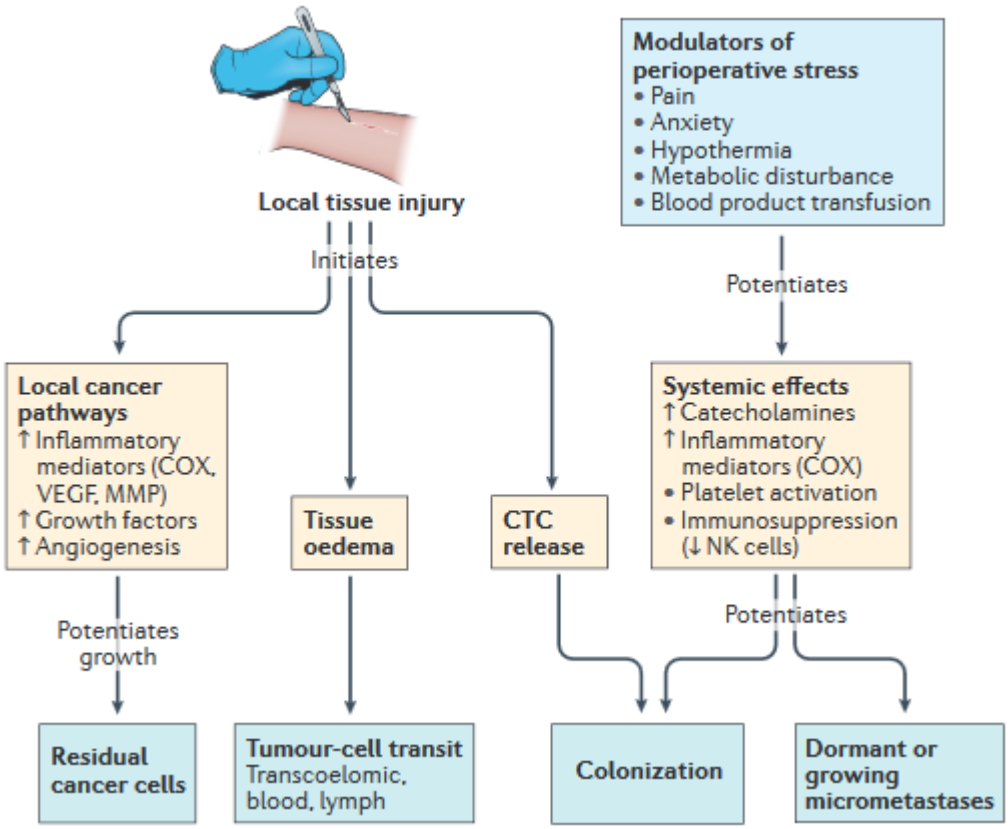
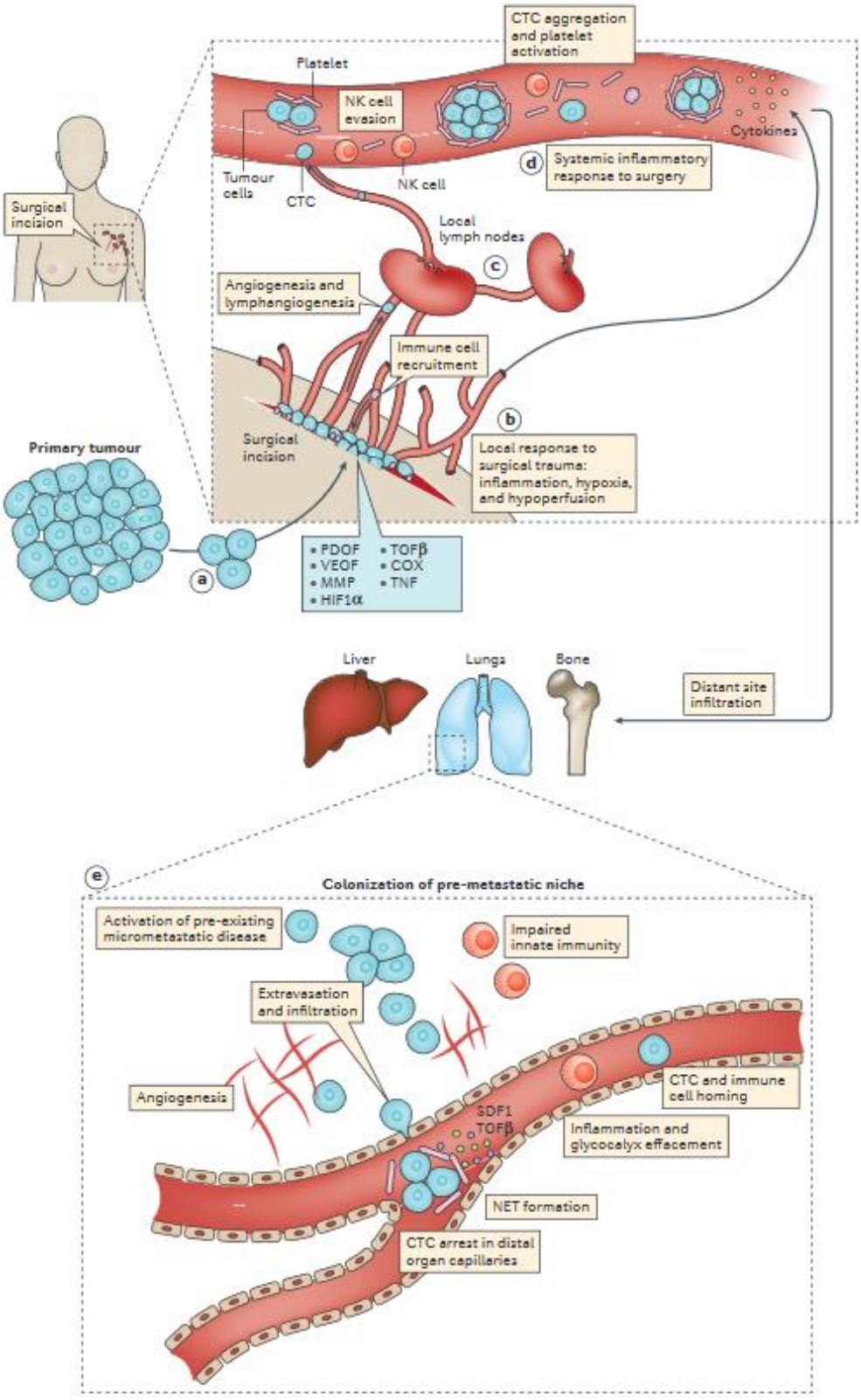

Local tissue injury
Modulators of perioperative stress
• Pain
• Anxiety
• Hypothermia
• Metabolic disturbance
• Blood product transfusion
Initiates
Potentiates
Local cancer pathways
↑ Inflammatory mediators (COX, VEGF, MMP)
↑ Growth factors
↑ Angiogenesis
Tissue oedema
CTC release
Systemic effects
↑ Catecholamines
↑ Inflammatory mediators (COX)
• Platelet activation
• Immunosuppression (↓ NK cells)
Potentiates growth
Potentiates
Residual cancer cells
Tumour-cell transit
Transcoelomic, blood, lymph
Colonization
Dormant or growing micrometastases

Figure 2


CTC aggregation and platelet activation
Platelet
NK cell evasion
Cytokines
Tumour cells
CTC
NK cell
d
Systemic inflammatory response to surgery
Surgical incision
Local lymph nodes
c
Angiogenesis and lymphangiogenesis
Immune cell recruitment
b
Surgical incision
Local response to surgical trauma: inflammation, hypoxia, and hypoperfusion
Primary tumour
a
• PDOF • TOFβ
• VEOF • COX
• MMP • TNF
• HIF1α
Liver
Lungs
Bone
Distant site infiltration
e
Colonization of pre-metastatic niche
Activation of pre-existing micrometastatic disease
Impaired innate immunity
Extravasation and infiltration
Angiogenesis
CTC and immune cell homing
SDF1
TOFβ
Inflammation and glycocalyx effacement
NET formation
CTC arrest in distal organ capillaries

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