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Review

Circulating biomarkers in perioperative management of cancer patients

Qiyuan Huang[1,2,§], Ruihao Zhou[1,2,§], Xuechao Hao[1,2], Weiyi Zhang[1,2], Guo Chen[1,2,*] and Tao Zhu[1,2,*]

[1]Department of Anaesthesiology, West China Hospital, Sichuan University, Chengdu 610041, China

[2]The Research Units of West China (2018RU012)-Chinese Academy of Medical Sciences, West China Hospital, Sichuan University, Chengdu 610041, China

*__Correspondence:__ Guo Chen, grace_chenguo@hotmail.com; Tao Zhu, 739501155@qq.com

[§]Qiyuan Huang and Ruihao Zhou contributed equally to this work.

Abstract

Owing to the advances in surgical technology, most solid tumours can be controlled by surgical excision. The priority should be tumour control, while some routine perioperative management might influence cancer progression in an unnoticed way. Moreover, it is increasingly recognized that effective perioperative management should include techniques to improve postoperative outcomes. These influences are elucidated by the different functions of circulating biomarkers in cancer patients. Here, circulating biomarkers with two types of clinical functions were reviewed: (i) circulating biomarkers for cancer progression monitoring, for instance, those related to cancer cell malignancy, tumour microenvironment formation, and early metastasis, and (ii) circulating biomarkers with relevance to postoperative outcomes, including systemic inflammation, immunosuppression, cognitive dysfunction, and pain management. This review aimed to provide new perspectives for the perioperative management of patients with cancer and highlight the potential clinical translation value of circulating biomarkers in improving outcomes.

Keywords: circulating biomarker, perioperative outcome, precision oncology, perioperative medication

Introduction

According to cancer statistics, in 2022,[1] 1 918 030 new cancer cases and 609 360 cancer deaths are projected to occur in the USA. Despite the value of radical surgery and multimodal curative approaches, a significant fraction of cancer survivors will eventually perish because of locoregional relapse or distant metastasis, suffering from poor recovery. It is increasingly recognized that the disease and its treatment are major determinants of quality of life.

Cancer patients are particularly vulnerable, owing to complicated perioperative medications, malnutrition, and psychological symptoms. The perioperative stress response and treatment stimulate the release of inflammatory mediators, catecholamines, and angiogenesis activators, which coincides with a period of immunosuppression.[2] Therefore, during and after surgery, dormant tumours or micrometastases can progress, and the postoperative outcomes of cancer patients can be influenced by perioperative strategies.

Considering the surgery-mediated tumour-promoting effects, the perioperative period is recognized as a window for surgery-associated dissemination of tumour cells.[3] Additionally, it is characterized by a surgical stress response, pharmacologically induced angiogenesis, and immunomodulation.[4,5] Perioperative treatment causes a favourable change for cancer cell invasiveness and formation of the tumour microenvironment (TME), leading to recurrence and distant reimplantation. However, the perioperative stress response is closely linked to postoperative outcomes. Inappropriate perioperative management could disturb the immune and neuroendocrine stress responses, leading to poor recovery.[6] To improve outcomes, several aspects of cancer patients should be taken into consideration, including local immune response and systemic inflammation,[6] higher risk of postoperative cognitive dysfunction (POCD),[7] and challenging perioperative cancer- and surgery-related pain management.[8,9]

In the past few decades, considerable effort has been devoted to exploring new biomarkers for the early diagnosis and prognosis of cancer. Circulating biomarkers are released molecules that are detectable in the blood. They can be objectively measured and evaluated as indicators of pathogenic processes, including cancer cell invasiveness, metabolism, tumour angiogenesis, and cancer-related immunosuppression.[10–13] Meanwhile, an increasing number of clinical studies have used outcomes related to the quality of recovery to evaluate promising biomarkers. Some circulating biomarkers are also closely linked to systemic inflammation, cognitive dysfunction, and perioperative pain management in patients.[14–18]

To provide opportunities for a precise perioperative strategy, this review reveals how circulating biomarkers were altered and offers a theoretical framework of their roles in predicting cancer progression and postoperative outcomes in cancer patients. Circulating biomarkers were divided into two groups to evaluate the following: (i) circulating biomarkers indicating the influence of perioperative management on cancer progression, and (ii) circulating biomarkers reflecting the influence of perioperative management on quality of recovery. With circulating biomarkers,

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physicians may have a unique window of opportunity to improve perioperative outcomes.

Circulating biomarkers in perioperative cancer progression of cancer patients

According to the widely known acquired capabilities of cancer,[19] cancer progression involves the enhancement of *in situ* cancer cell proliferation and viability (invasion and migration ability of cancer cells), immunosuppression associated with immunological surveillance escape, and changes in the microenvironment (both *in situ* and in newly colonized tissue). There have been increasing concerns that perioperative treatment may have direct or indirect influences on tumour spread in postoperative cancer patients[20] (Fig. 1).

Circulating biomarkers and anaesthesia-associated cancer cell malignancy

Pigment epithelium-derived factor (PEDF) is a secreted protein of the serine protease inhibitor family with promising therapeutic value. The association between the loss of secreted PEDF and the aggressive phenotype of cancer has been previously examined.[10] Recent research by Hu *et al.* revealed how propofol upregulated the PEDF expression and ultimately inhibited the malignancy of lung cancer cells.[21]

In contrast to the antitumour effect of PEDF, upregulation of serum cytokines owing to general anaesthetics may play a crucial role in the micrometastasis of cancer. Sevoflurane can activate the interleukin (IL)-6/Janus kinase/signal transducer and activator of transcription 3 pathway by increasing the plasma level of IL-6, leading to increased metastasis compared with when propofol is used.[22] Another commonly selected drug, midazolam, also regulates plasma IL-6 levels. Midazolam administration has been associated with the proliferation inhibition of pancreatic ductal adenocarcinoma cells and TME formation by reducing plasma proinflammatory cytokine levels [IL-6, C-C motif chemokine ligand 2 (CCL2), CCL3, and CCL5].[11]

Circulating biomarkers for deregulated cancer metabolism

Tumour cells favour a suitable metabolism for spreading and locating. A well-known cellular feature of cancer cells is 'the Warburg effect', which increases glucose consumption and glycolysis towards lactate despite adequate oxygen supply.[23] Therefore, there may be a significant association between glucose levels and cancer cell proliferation and progression.

Avoiding long periods of preoperative fasting is a key aspect of perioperative care for patients undergoing major surgery, according to the enhanced recovery after surgery (ERAS) protocols. However, serum proapoptotic ketone bodies activated by preoperative fasting lead to antitumour consequences,[24] and an elevated fasting blood glucose level is associated with a poor prognosis in lung cancer patients.[25] The glucose to lymphocyte ratio (GLR), which combines inflammatory factors with preoperative blood glucose, also has predictive value. GLR can be used for preoperative risk stratification in patients with pancreatic ductal adenocarcinoma as patients with a GLR > 3.47 have worse overall survival (OS) after radical surgery (area under the curve (AUC) = 0.6937).[26] Perioperative caloric intake activates anabolic metabolic networks that participate in proliferation and growth, mainly through the insulin signaling pathways. For example, preoperative per-oral carbohydrate load accelerates proliferation in breast cancers, which is associated with upregulated serum insulin and insulin c-peptide levels and downregulated serum insulin-like growth factor binding protein-3 levels.[27] These analyses relied on tumour tissue samples, and the metabolic consequences of the ERAS protocols at the individual level require further investigation.

Circulating biomarkers associated with tumor angiogenesis

Surgery and circulating biomarkers for angiogenesis

In breast cancer patients, mastectomy promotes a transient increase in the plasma levels of vascular endothelial growth factor (VEGF)-A and IL-8, while shifting the expression patterns of some angiogenesis-related circulating gene transcripts.[4] In non-small cell lung cancer patients, angiopoietin-2 levels increase after surgery and exhibit proangiogenic properties.[28] In addition to growth factor proteins, circulating tumour endothelial cells (cTECs) exhibit proangiogenic activity similar to that of circulating tumour cells (CTCs), and can contribute to angiogenesis in remote sites.[29] In pancreatic adenocarcinoma patients after radical surgery, $CD44^+$ cTEC levels are significantly elevated, which could be an independent predictor of shorter disease-free survival (DFS).[30]

Anaesthesia and circulating biomarkers for angiogenesis

Administration of lidocaine through propofol epidural anaesthesia decreased the serum concentration of VEGF-C, which is associated with angiogenesis during colon cancer surgery.[31] Galoș *et al.* reported no significant influences of intravenous lidocaine on VEGF or VEGF-A in breast cancer patients, likely due to the insufficient effect of a low dosage (1 $mgkg^{-1}h^{-1}$), and the observed VEGF expression level decrease might be attributable to propofol.[32] Differences in tumour histology could explain the inconsistent effects due to similar perioperative factors, as they may express VEGF differently.

CTCs link general anaesthetic to cancer progression

The presence of CTCs and CTC clusters in peripheral blood, supported by liquid biopsy techniques, has been identified as a promising indicator for assessing cancer progression.[33,34] Haematogenous tumour cell extravasation leads to the presence of CTCs in peripheral blood, particularly during surgical tumour resection.[35] In this respect, CTC monitoring may serve as an ideal approach to better understand the influence of perioperative management on distant metastasis.[12,13]

Whether anaesthesia type affects CTC counts in cancer patients remains unclear. One recently published large-scale randomized controlled trail (RCT) indicated that neither propofol nor sevoflurane would influence CTC counts over time (within 72 h), although administration of sevoflurane caused a significant increase in maximal tumour cell counts postoperatively.[36] Compared with count of pre-operative total CTCs, elevated post-operative total CTCs (≥6), showed more significant correlation with recurrence and metastasis.[37] Patients who are CTC-positive are at the risk of developing resistance to adjuvant chemotherapy and poor progression-free survival.[38] Long-term outcome analysis should at least cover the early peak of recurrence to confirm whether CTC counts act as reliable prognostic biomarkers for early recurrence.

In terms of preclinical evidence, some groups have employed experimental metastasis mouse models to investigate the influence of anaesthesia management on CTCs and the underlying

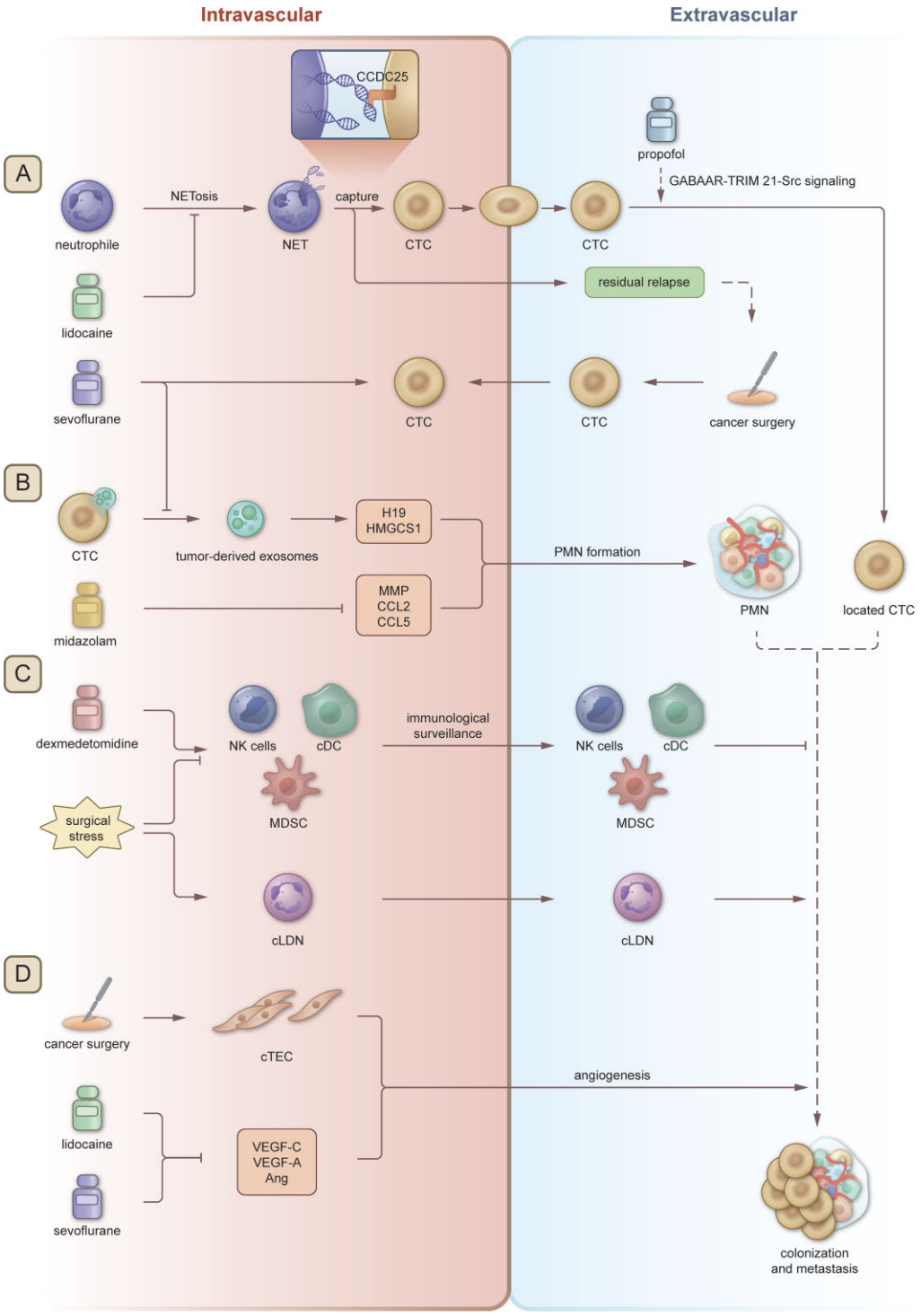

Figure 1. Perioperative management influences tumour progression via regulating circulating biomarkers in cancer patients. (**A**) Surgical manipulation directly increased the possibility of spreading CTCs into the bloodstream nearby, and administration of sevoflurane was associated with elevated total CTC count. NETs could capture CTCs and promote their adhesion to the endothelium. Propofol activated GABAAR-TRIM 21-Src signaling, endowing adhesion and extension of CTCs; NETs also awakened dormant cancer cells. Lidocaine inhibited NETosis and reduced the relapse rate indirectly. (**B**) Circulating tumour-derived exosomes regulated metastasis and colonization via convoying 'cargo' to the target organ. Inflammatory factors were closely related to PMN formation. (**C**) Circulating immune cells showed the significance of reflecting the activation or inhibition of immunological surveillance; dexmedetomidine alleviated immunosuppression by upregulating MDSC, cDC, and NK cells, while surgical stress was related to immunosuppression. cLDN increased by surgical stress facilitated the tumour colonization process. (**D**) Anaesthetics inhibited tumour-induced angiogenesis in cancer patients; additionally, a higher level of cTECs caused by surgery enhanced angiogenesis of metastatic tumours. Abbreviations: CTC, circulating tumour cell; NET, neutrophil extracellular trap; CCDC25, coiled-coil domain containing 25l; TRIM 21, tripartite motif-containing protein 21; H19, long non-coding RNA H19; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; MMP, metalloproteinase; CCL2, C-C motif chemokine ligand 2; CCL5, C-C motif chemokine ligand 5; PMN, pre-metastatic niche; NK, natural killer; cDC, circulating dendritic cell; MDSC, myeloid-derived suppressor cells; cLDN, circulating low-density neutrophils; VEGF, vascular endothelial growth factor; Ang, angiopoietin; cTEC, circulating tumour endothelial cells.

mechanism. A study reported that standard doses of propofol activated type-A γ-aminobutyric receptor–tripartite motif 21-Src signaling, resulting in adhesion and extension of CTCs to vascular endothelial cells. This mechanism may be involved in promoting tumour metastasis.[39]

Circulating biomarkers link perioperative immunosuppression to cancer progression

Patients with the three following sufficiently studied perioperative risk factors are likely to experience progression of minimal residual disease after surgery: (i) Decreased levels of tumour-related antiangiogenic factors (such as angiostatin and endostatin) caused by surgery-associated cell-mediated immunity inhibition;[5] (ii) Impaired postoperative natural killer (NK) cell function and elevated hypoxia inducible factor-1α activity owing to the consumption of inhaled anaesthetics;[40] (iii) The consumption of opioid analgesics that inhibit cellular and humoral immunity.[41]

The progression of minimal residual disease is majorly due to activated angiogenesis and a perioperative immunosuppressive environment. However, it is quite early to conclude that perioperative immunosuppression leads to recurrence. Studies with long-term follow-up or sub-studies based on data from a multicentre RCT have reported that types of anaesthesia (regional or general anaesthesia; regional paravertebral block combined with propofol or sevoflurane) have limited influence on the recurrence of breast cancer after surgery.[42,43]

Volatile anaesthetics and opioid analgesics suppress NK cell function

NK cells are the main defense mechanism against cancer metastasis. Increased NK cell counts in blood samples and the recovery of NK cell cytotoxicity (NKCC) have been associated with a lower risk of cancer recurrence.[44] Postoperative treatment helps recover NK cell function in breast cancer patients.[45] Volatile anaesthetic agents, including sevoflurane and desflurane, decrease NKCC,[46] while propofol does not suppress NKCC.[47,48] In terms of analgesia, fentanyl suppresses NK cell function,[49] but non-steroidal anti-inflammatory drugs reverse NKCC suppression.[50] Therefore, regimens that avoid volatile anaesthetics and opioid analgesics may have a favourable effect on innate immune function.[51]

Perioperative regulation of neutrophil function

Neutrophils degranulate on engagement with tumour cells, thereby 'trapping' them, and this immunologic response is called neutrophil extracellular trapping (NETosis).[52] Owing to its ability to ensnare moving cells, NETosis is an immunological mechanism that is strongly associated with increased metastatic risk.

In terms of anaesthesia management, local anaesthetics partly regulate granulocyte function, thereby modifying the immune responses in cancer patients. Kolle *et al*. observed that bupivacaine and lidocaine shortened the time to half-maximal NETosis in a dose-dependent manner.[53] Clinically, some patients are treated with lidocaine infusions to develop ERAS protocols. Systemic lidocaine infusion based on general anaesthesia can significantly reduce NETosis and cancer recurrence.[32] However, neither volatile general anaesthesia nor propofol-paravertebral regional anaesthesia (with levobupivacaine) affects NETosis expression in breast cancer patients.[54] Continuous intravenous administration of local anaesthetics, instead of paravertebral administration, may provide increased benefits for patients.

Recently, studies have demonstrated that the 'safety net' of neutrophils might not be 'safe' anymore, because CTCs might be summoned by NETs to settle and proliferate via a NET-DNA-receptor on tumour cells.[55,56] *In vivo* situations may be more complex because of various interferences. Future trials with long-term follow-up data are required to validate whether serum NETosis expression can be a reliable prognostic marker in cancer patients.

Additionally, surgical stress increases the level of circulating low-density neutrophils (cLDNs), which might favour the lodging of CTCs and inhibit T-cell response in target organs, contributing to postoperative metastasis.[57] Therefore, the administration of functional blockade of the cLDN might partly slow down the growth of minimal residual disease and improve the oncological outcomes of surgical patients.

Circulating biomarkers link perioperative management to the postoperative outcomes of cancer patients

For cancer patients, the first priority should be tumour control, while it is increasingly recognized that effective management of patients should include ERAS protocols to improve the outcome of surgery and quality of life. The main principle and purpose of the ERAS pathway depend on the attenuation of the stress response to surgery. Increased perioperative stress levels are closely linked to severe systemic inflammation,[14,58] hindered innate immune system reconstitution,[2] higher levels of neuroinflammatory responses,[59] and perioperative pain.[60,61] Hence, the mechanism through which perioperative management influences the outcomes of cancer patients and the kind of clinical functions circulating biomarkers play required comprehensive review.

Circulating biomarkers of perioperative systemic inflammation

Systemic inflammation can be a stage-independent marker of poor prognosis in some cancers. It is characterized by elevated levels of serum C-reactive protein (CRP), several proinflammatory cytokines, and systemic inflammation-based scores, including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII).[62,63]

From the perspective of haemodynamic fluctuations caused by anaesthesia, fewer fluctuations in anaesthesia management may trigger a lower degree of systemic inflammation. Compared to propofol, sevoflurane provides better haemodynamic stability, particularly in vulnerable patients who are at risk of a ventilation flow ratio imbalance. Alveolar and systemic inflammatory mediators have been observed in biospecimens of patients undergoing one-lung ventilation, especially in the ventilated lung.[58] Administration of sevoflurane during lung resection reduces the frequency of postoperative pulmonary complications.[14] Meanwhile, decreased serum IL-6, IL-10, and tumour necrosis factor alpha (TNF-α) levels indicate that sevoflurane attenuates pulmonary and systemic inflammatory responses.[14,58] Clinical data have demonstrated that general anaesthesia combined with epidural anaesthesia exerts anti-inflammatory effects, as measured by NLR, LMR, and SII, related to longer OS and DFS in cancer patients.[63,64]

There is a 'bidirectional causality' between pain and inflammation (Fig. 2). In cancer patients who undergo surgery, systemic or local inflammation caused by surgery worsens neuronal

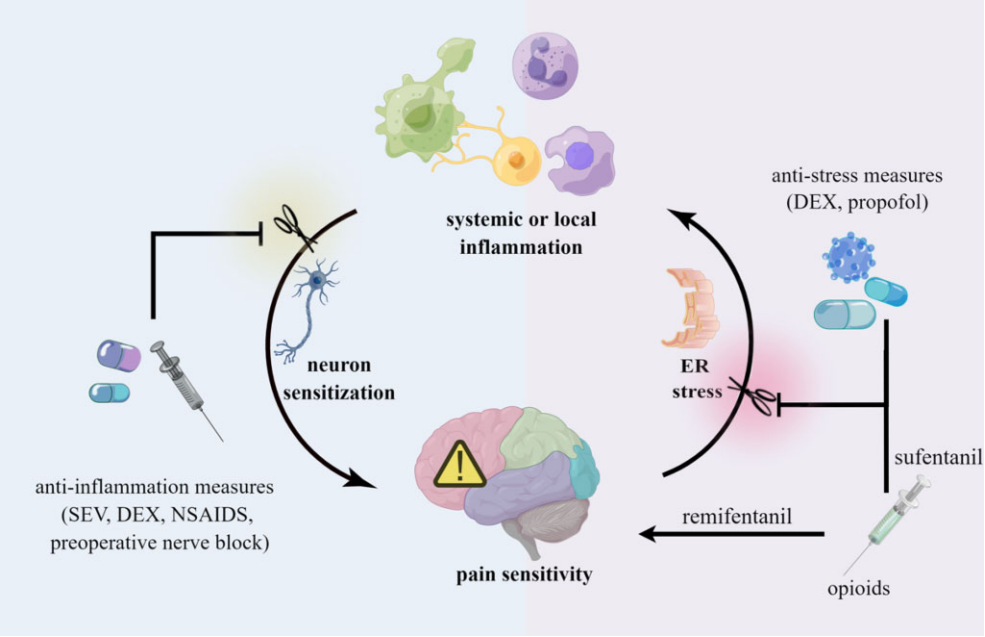

Figure 2. The 'bidirectional causality' between pain sensitivity and inflammation in cancer patients. Caused by cancer *per se*, preoperative chronic inflammation in cancer patients brought sensitization to peripheral pain-sensing neurons. Reversely, high pain sensitivity meant that the suprathreshold stimuli would cause abnormally worse stress responses linked to the release of inflammatory factors. Well-balanced perioperative management could help cut off these bidirectional bonds via selected analgesic and anti-inflammatory management. Abbreviations: SEV, sevoflurane; DEX, dexmedetomidine; NSAIDS, nonsteroidal anti-inflammatory drug; ER, endoplasmic reticulum.

sensitization, leading to hyperalgesia.[60,61] In contrast, an elevated level of systemic inflammation is largely because of oxidative stress and surgical pain caused by surgical trauma.[65,66] Dexmedetomidine,[67] propofol,[68] and sufentanil[69] help blunt surgical stress responses, particularly neuroendocrine-related responses. Simultaneously, relief of perioperative inflammation and pain would significantly facilitate the re-establishment of baseline homeostasis.

Circulating biomarkers indicating immunomodulation during postoperative recovery

Immunosuppression is an accepted hallmark of limited prognosis in cancer therapy. Perioperative immunomodulation not only participates in avoiding the immune destruction of cancer but also has diverse influences on the quality of recovery.

Intraoperative opioid administration can be the first choice for managing acute surgical pain but is unfortunately accompanied by a significant immunosuppression effect on NKCC, the activity of neutrophils and macrophages, and T lymphocyte proliferation.[70] Local anaesthetic administration reduces the demand for opioids, leading to alleviated perioperative immunosuppression and improved quality of recovery.[71]

Additionally, dexmedetomidine is usually used as a sedative and an adjuvant to anaesthetic strategies in the perioperative context. It can reduce the stress response and exert favourable effects on outcome improvement in radical surgeries of breast, colon, oral, and gastric cancer.[72–75] However, the direct and indirect effects of dexmedetomidine on residual disease should not be ignored. *In vitro* studies have shown that dexmedetomidine has the effect of increasing cell survival and cell proliferation,[76] while *in vivo* studies have reported both potentiation and lack of effect of dexmedetomidine on tumour progression.[77] We should be aware that the generalizability of the findings to cancer progression in humans is uncertain as the effect might differ between species.

Postoperatively, some opioid drugs exert unique immunostimulatory properties. For example, dezocine administration has been associated with the promotion of dendritic cell (DC) maturation and general immune response, as measured by circulating DC surface markers, IL-12, IL-6, and activated $CD8^+$ cells in postoperative blood samples from lung cancer patients.[78] In terms of patient-controlled intravenous analgesia for colorectal cancer patients, pharmacological options using oxycodone and flurbiprofen may be more favourable compared to those using sufentanil and flurbiprofen. This strategy can not only effectively reduce visceral pain but also promote $CD4^+$ T-cell function, leading to earlier recovery and reduced postoperative complications.[79] The question of whether alleviating immunosuppressive effects by selecting optimal opioid drugs could improve the long-term prognosis remains unanswered.

Circulating biomarkers of postoperative cognitive function of patients with cancer

Circulating biomarkers of POCD

With age as an independent risk factor, POCD may lead to worse consequences, such as delayed postoperative recovery, decreased quality of life, and a possible increased risk of Alzheimer's disease. Mechanically, studies on pathogenesis have hypothesized that POCD is caused by central cholinergic deficiencies that lead to abnormal facilitation of the neuroinflammatory response. Elevated serum levels of some circulating inflammatory markers, including CRP, calcium-binding protein (S-100), and IL-6, may predict the occurrence of POCD in elderly patients.[15,16]

Combined anaesthetic techniques that alleviate systemic inflammation contribute to reducing the risk of POCD. Therefore, dexmedetomidine is a better choice for POCD high-risk patients. Extensive high-level evidence from meta-analyses has demon-

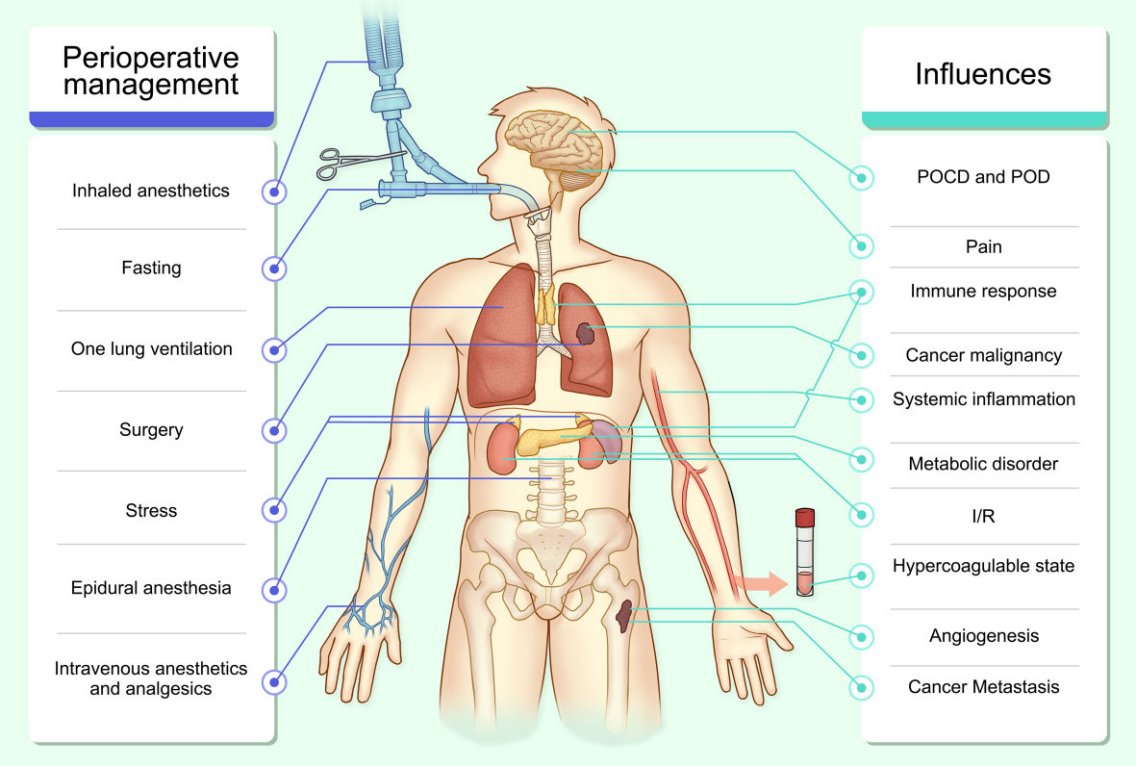

Figure 3. The influences of perioperative management on cancer patients. Many systems were involved including the central nervous system, immune system, respiratory system, endocrine system, blood system, etc. The disturbance of the fragile balance of each system could be reflected through the change of certain circulating biomarkers. Abbreviations: POCD, postoperative cognitive dysfunction; POD, postoperative delirium; I/R, ischemia and reperfusion.

strated that dexmedetomidine may exert sympatholytic, anti-inflammatory, or neuroprotective effects, thereby decreasing the incidence of POCD.[80,81] In elderly patients with esophageal carcinoma, dexmedetomidine reduced the incidence of POCD caused by sevoflurane inhalation anaesthesia and decreased plasma TNF-α, IL-6, and S100 calcium-binding protein B (S-100β) protein concentrations.[82]

Circulating biomarkers of postoperative delirium

The incidence of postoperative delirium (POD) in the general surgical population is 2%–3%, and it has been reported to occur in up to 48% of high-risk elderly patients.[83] Surgery, as the 'second hit', amplifies existing neuroinflammation in high-risk patients. Several inflammatory biomarkers can predict POD in cancer patients, particularly in the elderly. In terms of S-100β, limited research has elucidated the prognostic value of serum S-100β as a biomarker of delirium in cancer patients. Mietani *et al*. reported that serum S-100β could predict axonal damage associated with delirium in patients who undergo surgery for cancer[84], while a meta-analysis by Zhang *et al*. showed that the S-100β level in cerebrospinal fluid may exert more clinical significance than serum S-100β.[85] However, poor universality hampered the clinical application of S-100β levels in cerebrospinal fluid owing to the high-risk of the invasive procedures required to obtain samples.

Strong evidence suggests that perioperative administration of dexmedetomidine can significantly reduce the incidence of POD in elderly patients following non-cardiac surgery (at least 42.2% of patients enrolled were diagnosed with cancer).[86] Some of these studies on dexmedetomidine selected biomarkers as secondary outcomes, including serum IL-2, IL-6, IL-8, IL-10, TNF-α, CRP, and brain-derived neurotrophic factor (BDNF).[17] In elderly colorectal cancer patients, dexmedetomidine-assisted anaesthesia is beneficial to postoperative cognitive function by reducing cerebral oxygen metabolism. Serum interferon-γ, myelin basic protein, neuron-specific enolase (NSE), and S-100β levels predict the cognitive function of patients and the occurrence of adverse reactions.[87] Accordingly, patient-controlled epidural analgesia (levobupivacaine) results in a lower level of some inflammatory markers and a lower incidence of POD compared with intravenous morphine analgesia (92% of the patients enrolled were pathologically diagnosed with cancer).[88]

Predictive metabolic biomarkers for postoperative cognitive function

Metabolomics allows dynamic monitoring of transient biochemical changes that are influenced by various environmental and pathological stimuli.[89,90] In blood samples from patients with gastrointestinal tumours, phosphatidylserine (17:2/0:0) is a potentially sensitive and specific circulating biomarker for the diagnosis and prognosis of POCD (AUC 0.966).[91] In the meantime, deficiencies of ω3 and ω6 fatty acids and disorders in aromatic amino acid and branched-chain amino acid metabolism aggravate the vulnerability of the aging neurotransmitter systems in high-risk POD patients. Targeted metabolomics analysis indicated that another 11-metabolite prediction model helped predict POD in elderly patients undergoing major noncardiac surgery (AUC 0.838).[92] Future investigations of biomarkers for the derangement of functional systemic metabolism may reveal their promising specificity.

Table 1. Circulating biomarkers link perioperative management to cancer progression and postoperative outcomes.

Biomarker function	Circulating biomarker	Influence factor	Outcome	Cancer type
Angiogenesis	VEGF-C↓	Sevoflurane	A decrease in serum VEGF-C level; no significant benefit for short-term prognosis	Breast cancer
Angiogenesis	VEGF-C↓	Lidocaine	Decreased serum VEGF-C levels during colon cancer surgery	Colon cancer
Angiogenesis	Angiopoietin-2↑	Surgery	Proangiogenic property exerts (*in vitro*)	NSCLC (cell line)
Angiogenesis	Circulating TECs↑	Surgery	Patients with shorter DFS	Pancreatic ductal adenocarcinoma
Angiogenesis	VEGF-A↑ IL-8↑	Surgery	A transient increase in plasma levels of angiogenesis-related circulating gene transcripts	Breast cancer
Cancer cell malignancy	PEDF↓	Propofol	Inhibited malignancy	Lung cancer
Cancer cell malignancy	IL-6↓ CCL2, CCL3, and CCL5↓	Midazolam	Inhibition of cell proliferation and TME formation	Pancreatic ductal adenocarcinoma cell
Cancer cell malignancy	Exosomal circ-HMGCS1↓	Sevoflurane	Inhibited cell viability and invasion but facilitated cell apoptosis	Colon cancer
Cancer cell malignancy	Exosomal lncRNA H19↓	Propofol	Inhibited proliferation, migration, and invasion; promoted apoptosis	Hepatocellular carcinoma
Cancer metastasis	IL-6↑	Sevoflurane	More lung metastasis	Breast cancer (mouse model)
Cancer metastasis	Maximal CTC counts↑	Anaesthetic techniques	N.S. (sevoflurane VS propofol anaesthesia)	Breast cancer
Cancer metastasis immunosuppression	Circulating LDNs↑	Surgical stress	More lodging of circulating tumour cells and inhibited T cell response	Gastric cancer
Metastasis-associated granulocyte defense	Serum NETosis↓	Systemic lidocaine infusion	Reduce NETosis and cancer recurrence	Breast cancer
Metastasis-associated granulocyte defense	Serum NETosis↓	Surgical stress	Reduced risks of liver metastasis	Colorectal carcinoma
Metastasis-associated granulocyte defense	Serum NETosis	Anaesthetic techniques	N.S. (volatile VS propofol general anaesthesia)	Breast cancer
NK cell function	NK cell count	Anaesthesia types	N.S. (inhalation anaesthesia vs TIVA)	Kidney cancer
NK cell function	NKCC↓	Sevoflurane and desflurane	Increased susceptibility to tumour metastasis	Breast cancer (rat model)
NK cell function	NKCC↓	Sevoflurane	Inhibited cancer immunosurveillance and metastasis	NSCLC (cell line)
NK cell function	NKCC↓	Fentanyl	Decreased resistance to tumour metastasis	Breast cancer (rat model)
NK cell function	NKCC↑	Propofol with postoperative ketorolac analgesia	Less recurrence	Breast cancer
Systemic inflammation	IL-6, IL-10, and TNF-α↓	Sevoflurane and OLV	Reduced pulmonary and systemic inflammatory response; more post-operative complications	Lung cancer
Systemic inflammation	IL-8;IL-6;CRP;TNF-α↓ SOD;Glutathione;CAT↑	Remifentanil	Less postoperative adverse reactions	Colon cancer
Systemic inflammation	Bone morphogenetic protein 4↓	Flurbiprofen	Alleviated IL-1β and TNF-α release	Lung cancer
Systemic inflammation	NLR, LMR, SII↓	Epidural anaesthesia	Patients have longer OS and DFS	Hepatocellular carcinoma
Systemic inflammation	NLR↓	Epidural anaesthesia	Have not discussed (ongoing project)	Breast cancer

Table 1. (*Continued*)

Biomarker function	Circulating biomarker	Influence factor	Outcome	Cancer type
Local inflammation	Proinflammatory cytokines↑	OLV	Promoted local inflammation in the ventilated lung	Lung cancer
Immunosuppression	IL-12↓ Circulating pDCs↓	Surgical stress	Inhibited immune-stimulatory interventions and abolished metastasis-reducing impacts.	Colon tumour (rat model)
Immunosuppression	Interferon-gamma-inducible protein 10 (IP 10), granulocyte colony-stimulating factor (G-CSF), and IL-6↑; circulating MDSCs ↓	Perioperative stress	Enhanced immune function	Breast cancer
Immunosuppression	Circulating MDSCs↓	Mastectomy-associated stress	Lower postoperative VAS score	Breast cancer
Immunosuppression	Circulating MDSCs	Anaesthesia technique	N.S. (sevoflurane-based anaesthesia and propofol-based TIVA)	Breast cancer
Immunosuppression	NK cells, T cells	Anaesthesia technique	N.S. (propofol-based anaesthesia vs volatile anaesthetics-based anaesthesia)	Colorectal cancer
Immunosuppression	Total lymphocytes↓	Local anaesthesia	Lower impact on postoperative lymphocyte response	Breast cancer
Immunosuppression	Hallmarks of immunogenic cell death↑	NSAIDs	Restored immunosurveillance and suppressed colorectal tumour formation	Colorectal cancer
Immunosuppression	$CD3^+$cells↑ $CD4^+$cells ↑ DCs↑ $CD4^+/CD8^+$ratio↑	Dexmedetomidine	Alleviated immunosuppression	Oral cancer
Immunosuppression	TNF-a↓IL-6↓ Th1/Th2 balance	Dexmedetomidine	Reduced inflammatory responses; lower VAS score	Gastric cancer
Immunosuppression	$CD4^+/CD8^+$↑ NK cells↑ INF-gamma, IL-2, IL-10, IL-6↑	Dexmedetomidine	Dexmedetomidine maintains the homeostasis of cell immune function	Breast cancer
Immunosuppression	DCs surface markers↑	Dezocine	Dezocine promotes the morphological maturation of DCs	Lung cancer
Immunosuppression	$CD4^+/CD8^+$ratio↑	PCIA (oxycodone combined with flurbiprofen axetil)	Less postoperative adverse reactions; reduced pain intensity; alleviated immunosuppression status	Colorectal cancer
Pain	Dopamine (DA), neuropeptide Y (NPY), substance P (SP)↓	Dezocine and ropivacaine	Reduced stress response, immune function fluctuations, and shortened recovery time	Hepatocellular carcinoma
Pain	β-EP↑	Electroacupuncture	Pain relief but breast cancer progression	Breast cancer
Prediction of analgesic efficacy	miRNAs indicating μ-opioid receptor signal	Hydromorphone	Patients with low MOR signals achieved better pain control through hydromorphone	Patients with cancer pain
Postoperative cognitive function	S-100 protein↓	Dexmedetomidine	Less adverse responses and less occurrence of POCD brain protection effect	Gynaecological cancer
Postoperative cognitive function	Brain-derived neurotrophic factor (BDNF)	Dexmedetomidine	Dexmedetomidine reduced cognitive decline up to one postoperative month in elderly patients	Gastrointestinal tumours
Postoperative cognitive function	Phosphatidylserine (PS) (17:2/0:0)	Surgery	New diagnostic biomarkers for POCD (AUC = 96.6%)	Gastrointestinal tumours

Table 2. Techniques for novel circulating biomarkers detection.

Technique	Circulating biomarker	Parameters assessed	Key features
Flow cytometric analysis	cLDN	♦ $CD66b^+$	♦ Convenient ♦ High efficiency
	pDC	♦ CD83, CD40, CD80, CD86, HLA-DR	
	cMDSC	♦ CD14, HLA-DR, PERCP-Cy5.5-A, etc.	
	NK cell	♦ $CD3^-/CD16^+/CD56^+$	
	NKT cell	♦ $CD3^+/CD16^+/CD56^+$	
SE-iFISH platform	cTEC	♦ $CD44^+$	♦ Independence of the expression of cell surface markers of tumour cells
CytoTox 96® Non-Radioactive Cytotoxicity Assay Kit	NKCC	♦ LDH activity ♦ Formazan optical density	♦ Rapid and objective determination ♦ Non-radioactive ♦ Quantitative study
CellSearch assay	CTC	♦ $EpCAM^+/CK^+/DAPI^+/CD45^-$	♦ FDA-approved
ELISA	NETosis	♦ MPO and H3Ci	♦ High specificity ♦ High objectivity ♦ High quantitative
ExoQuick kit	Exosome	♦ PEG	♦ No additional equipment required
Liquid chromatography Q-TOF MS	Metabolic biomarker	♦ Serum metabolites	♦ Muti-target detection for metabolites ♦ Precise quantification and identification

Abbreviations: SE-iFISH, immunostaining-fluorescence *in situ* hybridization; Q-TOF MS, quadrupole time-of-flight mass spectrometry; ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug Administration; LDH, lactate dehydrogenase; EpCAM, epithelial cell adhesion molecule; DAPI, 4',6-diamidino-2-phenylindole; MPO, myeloperoxidase; PEG, poly-ethylene glycol.

Circulating biomarkers to aid perioperative pain therapeutics in patients with cancer

Clinically, pain assessment and analgesic effects are indirectly measured via scales, including the visual analogue scale (VAS), numerical analogue scale (NAS), or via individualized questionnaires owing to the subjective nature of pain. In some ways, objective detection of circulating biomarkers not only reflect pain relief but also predict postoperative pain and analgesic efficiency. For example, preoperative administration of dezocine and ropivacaine decreased serum pain factors, including dopamine, neuropeptide Y, and substance P in patients anticipating liver cancer resection.[18] Acupuncture-assisted anaesthesia shortened the recovery time of anaesthesia, relieved the surgical side effects, and improved recovery by upregulating the serum level of beta-endorphin (β-EP) in stomach cancer patients.[93] However, whether the benefit of increased β-EP level outweighs the increased risk of cancer progression[94] requires further elucidation.

In addition to pain factors, as reviewed above, estimation of analgesic efficacy could optimize pain management with opioids. Profiling plasma miRNA signatures of cancer patients, including hsa-miR-423–3p, hsa-let-7a-5p, hsa-miR-26a-5p, etc., aids in estimating the potential for further mu-opioid receptor stimulation by opioid treatment, especially for patients suffering from chronic cancer pain.[95] However, different opioid treatments may result in different signatures of circulating miRNAs, which necessitates the development of personalized miRNA models to evaluate the analgesic efficacy of opioids.

Discussion

As reviewed here, perioperative management primarily influences the recurrence and metastasis of cancer and the short-term outcomes of cancer patients (Fig. 3). The potential for circulating biomarkers can be tumour-informed or -uninformed depending on the goals of its use (Table 1).

Perioperative management influences cancer progression. Key mechanisms include the spread of CTCs, TME formation, and immunosurveillance regulation: (i) The administration of general anaesthetics promotes the spread of CTCs but inhibits tumour-induced angiogenesis. (ii) Perioperative stress and inflammation favour TME formation, while some benzodiazepines exhibit anti-inflammatory effects and inhibit tumour progression. (iii) Surgical manipulation and the perioperative stress response are closely related to tumour-associated immunosuppression,[5] and administration of dexmedetomidine alleviates immunosuppression.[67] Multi-omic networks are altered in the perioperative period and influence cancer progression, and the following circulating biomarkers are noteworthy: PEDF, IL-6, CCL2, GLR, CTCs, and NETosis.

Perioperative management influences postoperative outcomes by regulating the perioperative stress response. However, how perioperative stresses transmit information and alter elements of the molecular profile such as RNA and protein expression is not yet understood. Limited recovery of immune function, systemic inflammation, cognitive dysfunction, and poor pain management are highly discussed indicators of poor postoperative outcome. During the perioperative period, circulating biomarkers have the following functions: (i) monitoring the suppression and recovery of cellular immunity through the NK cell count, $CD4^+/CD8^+$ ratio, and TNF-α level; (ii) predicting systemic inflammation through IL-6, TNF-α, and superoxidedismutase (SOD) levels; (iii) identifying patients with a high risk of cognitive dysfunction through S-100 protein, NSE, and BDNF levels; and (iv) prediction of patients' response to certain opioid through miRNAs profiling and signatures including hsa-miR-423–3p.

Inflammatory pathways are often activated during the perioperative period, resulting in unfavourable postoperative outcomes. The regulation of inflammation-related networks modifies cancer

Table 3. Clinical validation of circulating biomarkers: ongoing trails (up to January 2023).

Clinical value	Circulating biomarker	Interventions	Study title	N of Patients	Conditions	Identifier (status)
Diagnostic	ctDNA	♦ Diagnostic test	Evaluation ctDNA in patients of non-small-cell lung cancer following resection	200	NSCLC	NCT04238130 (Recruiting)
Diagnostic	CTCs, tdEVs, ctDNA	♦ Diagnostic test	Circulating biomarkers for individualized surgical therapy in gastroesophageal cancer—Phase 1	100	Esophagogastric	NCT04455282 (Not yet recruiting)
Diagnostic	TnI, NT-proBNP	♦ Diagnostic test	Perioperative troponin I and NT pro-BNP in lung resection	345	Lung cancer	NCT04749212 (Not yet recruiting)
Prognostic	IL-6, CRP, VEGF, etc.	♦ Propranolol and etodolac ♦ Placebo	Perioperative intervention to reduce metastatic processes in pancreatic cancer patients undergoing curative surgery (BC-PC)	210	Pancreatic adenocarcinoma	NCT03838029 (Recruiting)
Prognostic	CTCs	♦ Propofol ♦ Sevoflurane	Effects of TIVA versus inhalational anaesthesia on circulating tumour cells in hepatocellular carcinoma patients	220	Hepatocellular carcinoma	NCT04601961 (Recruiting)
Prognostic	IGFR, Bcl-2, Bcl-6	♦ Lidocaine 1% ♦ Sevoflurane ♦ Propofol	Elucidation of the mechanisms and effects of certain anaesthetic interventions on digestive cancer patients subjected to surgery	40	Colorectal cancer	NCT04162535 (Recruiting)
Prognostic	NLR, ctDNA, CTCs, cytokines, etc.	♦ Sevoflurane ♦ Propofol ♦ Lidocaine I.V. ♦ Placebo	Volatile anaesthesia and perioperative outcomes related to cancer: The VAPOR-C Trial	5736	Colonic cancer Rectal cancer NSCLC	NCT04316013 (Recruiting)
Prognostic	Cytokines	♦ Laparoscopic ALPPS ♦ Open ALPPS	Clinical outcome and future liver remnant regenerative response in laparoscopic versus open ALPPS	20	Liver cancer	NCT04868149 (Recruiting)
Prognostic	ctDNA, cytokines, etc.	♦ Robotic pancreatico-duodenectomy ♦ Open pancreatico-duodenectomy	Robotic versus open pancreaticoduodenectomy for pancreatic and periampullary tumors	244	Pancreatic adenocarcinoma	NCT04400357 (Recruiting)
Guide clinical treatment	AR-V7	♦ AR-V7 biomarker-guided personalised clinical treatment ♦ Standard care	VARIANT: A multicenter randomized feasibility trial of implementing a biomarker-guided personalized treatment in patients with advanced prostate cancer	70	Advanced prostate cancer	ISRCTN10246848 (Recruiting)
Guide clinical treatment	Tie2	♦ Treatment with VEGF Inhibitors	Validation of Tie2 as the first tumour vascular response biomarker for VEGF inhibitors: VALTIVE1	176	Ovary cancer	NCT04523116 (Recruiting)
Guide clinical treatment	cell-free DNA	♦ Blood-based cfDNA qPCR assay	Development and validation of a qPCR cell free DNA assay as a potential biomarker for predicting early non-response to therapy in metastatic cancer	750	Three types of metastatic cancer	NCT03892096 (Not yet recruiting)

Abbreviations: tdEVs, tumour-derived extracellular vesicles; IGF1R, insulin-like growth factor 1 receptor; Bcl-2, B cell lymphoma-2; Bcl-6, B cell lymphoma-6; NF-κB, nuclear factor-kappaB; ALPPS, associated liver partition and portal vein ligation for staged hepatectomy.

progression and improves postoperative outcomes[11,17,22,82,96,97] and even functions as a novel chemopreventive approach for cancer.[98]

The wave of multi-omic molecular networks has now reached anesthesiology, although many challenges remain, particularly concerning the detecting technology, development and translation of biomarker groups, tumour heterogeneity, and patient-centred outcome improvement. First, the discovery of novel circulating biomarkers is still in progress and relies on technological development (Table 2). Detection techniques with iterative refinement, such as liquid biopsy, miRNA-seq[99] or whole-blood miRNA profiling,[100] mass cytometry (CyTOF), and single-cell proteomics, will aid in investigation of novel circulating biomarkers for precise medicine. A personalized molecular profile for each cancer patient predicts or modifies preoperative risk for surgical and drug complications, offering a framework for future precision medicine. Second, network biology, combining a group of circulating biomarkers with diverse or specific functions, shows greater clarity and significantly improves the ability to understand, predict, and prevent disease. Additionally, novel circulating biomarkers improves the clinical value of routinely measured cancer biomarkers.[100] Artificial intelligence, especially machine-learning techniques, can be used to identify prognostic signatures in cancer patients.[101,102] Third, various types of cancer have been discussed in this review, with breast, colon, and lung cancers constituting the majority. The heterogeneity and bias attenuated the power of general conclusions. Notwithstanding, the mechanism of progression and perioperative stress response in patients with different types of cancers might be comparatively homogenous, providing opportunities for improving postoperative outcomes. Future research could explore the characteristics of circulating biomarkers in a population with a specific subtype and stage of cancer.[103] Fourth, an increasing number of prospective trials are validating the influences of different perioperative strategies and linking circulating biomarkers with a variety of outcomes (Table 3). More patient-reported outcomes should be assessed perioperatively to enhance efficiency and share decision-making.[104]

It is complicated to estimate the benefit of profiling circulating biomarkers for controlling cancer progression and improving postoperative outcomes of cancer patients, but it is evident that its impact is increasingly pervasive throughout medicine. Rather than relying on the outcome of only one circulating biomarker, the complementary results obtained through co-isolation and -analysis of the combination of biomarkers are likely to improve validity and precision in cancer monitoring, and ultimately will provide opportunities for precise perioperative strategies for individual cancer patients.

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Conflict of interest

None declared.

Authors' contributions

Q.H. conceived of the work and prepared the manuscript. R.Z. provided substantive editing and was a major contributor to writing the manuscript. X.H. and W.Z. provided critical review. T.Z. and G.C. were accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work were appropriately investigated and resolved. All authors read and approved the final manuscript.

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