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Review Article

The effects of anesthesia on cancer progression and anti-tumor immunity. A review

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Abstract

Introduction: Breast cancer is one of the most common malignancies, treated with primary surgery, or surgery after neoadjuvant chemotherapy. Many studies indicate that the peri-operative period is critical as interference with the immune system may affect prognosis. Whether certain anesthetic agents can affect the immune response and cancer progression is still unresolved.

Evidence acquisition: In the current study, we review the existing clinical and experimental studies, in an attempt to extract useful information for clinical application in the anesthesia practice for patients treated with surgery for breast cancer. A bibliographic search in PubMed and ScienceDirect related to the effects of anesthesia on cancer progression and anti-tumor immunity, published from January 2000 till today was performed.

Evidence synthesis: All included studies were gathered in a list and they were analysed. A total of 34 studies were found relevant to the subject in PubMed and ScienceDirect.

Conclusion: The overall experience suggests that the peri-operative management of cancer patients should focus on the reduction of surgical stress, the minimization of the use of opioids, and the adoption of regional anesthetics. This could have an impact on anti-tumour immunity and the outcome of cancer patients.

Introduction

Breast cancer is one of the most common malignancies, with approximately 2.2 million new patients and more than 680,000 deaths worldwide every year [1]. The gold standard in breast cancer treatment includes partial mastectomy or modified radical mastectomy with lymph dissection combined with chemotherapy and locoregional radiotherapy. Many studies indicate that the perioperative period is critical in primary cancer therapy because many factors can lead to alterations, either through surgical inoculation and the spread of tumor cells or because of interference with the immune system [2,3].

Whether certain anesthetic agents can also affect cancer progression is still unresolved. Some retrospective studies and meta-analyses suggest, that there is a correlation between the anesthesia technique, cancer-related mortality, and disease recurrence as a result of peri-operative immunosuppression induced in cancer patients [4].

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Here, we review clinical and experimental studies on anesthesia-related parameters in cancer patients that may affect the immunological anti-tumor response and tumor progression. The literature search was performed in the EMBASE and MEDLINE databases using the text words "anesthesia," "immune response," and "cancer". Both clinical and experimental studies have been evaluated and included.

Materials and methods

A bibliographic search in PubMed and ScienceDirect related to the effects of anesthesia on cancer progression and anti-tumor immunity, published from January 2000 till today was performed. The search was performed by combining the following terms: "anesthesia and immunity in cancer," "cancer and anesthetic agents," and "anesthesia and tumor progression." Our search criteria and inclusion/exclusion criteria were optimized to reduce doubt common in observational studies. The inclusion criteria were formed as follows: (1) randomized controlled trials and retrospective studies; (2) tumor patients, experimental studies in animals with cancer or *in vitro* cancer cells; (3) retrospective studies with adults 18 years or older; (4) studies showing an effect of anesthetic and analgesic agents in tumor progression and immune response (5) studies published in English; and (6) studies with an abstract. All titles and abstracts were first screened to identify and exclude studies according to the mentioned criteria. All included studies were gathered in a list and they were analyzed. A total of 29 studies were found relevant to the subject in PubMed and ScienceDirect (Table 1).

Results

Effect of surgical stress

Surgery remains a standard policy in the treatment of cancer. During surgery, however, tumor inoculation and metastasis may occur during the resection of the primary tumour [5]. In an *in vivo* experimental study with a breast cancer model, the surgery itself promoted tumor growth, and tumor spread through increased Matrix Metalloproteinase 9 (MMP-9) and Vascular Endothelial Growth Factor (VEGF) expression [6]. These experimental observations have been supported by clinical studies, where an increase of the VEGF levels in the blood of breast cancer patients during mastectomy was noted [7]. Moreover, acceleration of metastasis through the proliferation of pre-surgery established small inactive micro-metastases in distant sites is facilitated by the surgical stress [8].

Surgical injury activates a complex cascade of cytokine response involving pro-inflammatory and anti-inflammatory interleukins and interferons, affecting cellular immune responses and, eventually the anti-tumor immune surveillance [9]. The transient inhibition of immune function occurring as a response to the peri-operative stress is the main reason for postoperative infections, growth of residual cancer cells, and metastasis [10]. Specialized T-cells can inhibit or decrease the activation of the anti-tumor immune response or even disable the normal immune system [11]. The surgical stress leads to a decreased immune response, particularly by suppressing the

Table 1: Summary of studies showing the effect of anesthetic and analgesic agents on tumor progression and immune response.

Reference	Type of Study	Material	Technique / Drugs	Outcome
Clinical studies				
Bortsov, et al. 2012 [44]	Retrospective	Breast cancer (n = 2039 women)	Opioids	G allele results in reduced receptor transcription and response to opioid receptor binding. Women with G allele had decreased breast cancer-specific mortality (p < .001). Opioid pathways may be involved in tumor growth
Buckley, et al. 2014 [63]	Randomized controlled trial	Breast cancer patients (n = 10)	Propofol-paravertebral block (PPA) vs sevoflurane-opioid general anesthesia (GA)	GA subjects reduced NK cell activating receptor CD16 (P = 0.001), IL-10 (p = 0.001), and IL-1β (p = 0.01)
Deegan, et al. 2009 [31]	Randomized controlled trial	Breast cancer surgery, MDA-MB-231 (Adenocarcinoma cell lines)	Propofol/paravertebral (n = 11) or sevoflurane GA + opioid analgesia (sevoflurane/opioid, n = 11)	the proliferation of MDA-MB-231 in the Propofol/paravertebral group was significantly reduced compared with the sevoflurane/opioid group (p = 0.01)
Deegan, et al. 2010 [28]	Randomized controlled trial	Breast cancer surgery	Propofol/paravertebral (n = 15) or sevoflurane/opioid (n = 17)	Propofol/paravertebral group showed a greater decrease postoperative compared with preoperative IL-1β (p = 0.003), a significant attenuation in elevated MMP-3 (p = 0.011) and MMP-9 (p = 0.02), and a significant increase in IL-10 (p = 0.001)
Desmont, et al. 2015 [65]	Randomized controlled trial	Breast cancer patients (n = 20)	standard GA group vs Propofol-paravertebral group (PPA)	CD4 levels were lower in the GA group compared to the PPA group (p = 0.03)
Dong, et al. 2012 [64]	Randomized controlled trial	Ovarian cancer patients (n = 61)	general/epidural anesthesia (study group) or general anesthesia alone (control group)	The study group had significantly higher levels of IL-10 and IFN-γ (p < 0.001 and p = 0.017, respectively), and significantly lower levels of IL-1β and IL-8 (p = 0.003 and p = 0.020, respectively) at T_{4h} compared with the control group.
Exadaktylos, et al. 2006 [61]	Retrospective	Mastectomy and axillary clearance for breast cancer	GA+PPA (n = 450) GA+opioid analgesia (n = 479)	A 4-fold decrease in cancer recurrence in PPA group 2.5–4 years follow-up
Levins, et al. 2018 [45]	Randomized control trial	Breast cancer (n = 20)	PPA with continuing analgesia (PPA, n = 10) or balanced general anesthetic with opioid analgesia (GA, n = 10)	MOR levels were significantly increased in the GA intraoperative samples (p = 0.04)

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Lim, et al. 2018 [33]	Randomized control trial	Breast cancer surgery (*n* = 47)	Two groups: Propofol- or sevoflurane-based anesthesia	No difference in NK cell count, cytotoxic T lymphocyte count, or apoptosis rate was detected between the groups
Montagna, et al. 2021 [54]	Retrospective	Triple-negative breast cancer (*n* = 1143)	Fentanyl, hydromorphone and morphine	higher intraoperative opioid dose was associated with favorable recurrence-free survival, hazard ratio of 0.93 (95% confidence interval 0.88-0.99).
Singleton, et al. 2014 [43]	Retrospective	Non-small-cell lung cancer biopsy (*n* = 34)	MOR staining intensity in patient control, total lung cancer, and subset of lung cancer with lymph node metastasis	Significant difference in staining intensity between total lung cancer and the subset of total lung cancer with lymph node metastasis ($p = 0.0013$)
Zhang, et al. 2022 [53]	retrospective	Breast cancer patients (*n* = 80)	remifentanil and dexmedetomidine vs remifentanil (control group)	1 h during operation and 24 h after operation, the ratio of CD4+ and CD4+/CD8+ cells in the research group was significantly higher than that of the control group ($p < 0.05$)
Experimental studies				
Bimonte, et al. 2015 [42]	Experimental	MDA.MB231 Cells (late-stage breast cancer cell line)	Morphine	Enhancement of proliferation in breast cancer cells treated with morphine concerning control cells (*p* value < 0.05)
Chang, et al 2014 [56]	*In vitro*	Human breast cancer (MCF-7) and mammary epithelial (MCF-10A) cell lines	lidocaine and/or bupivacaine	Lidocaine and bupivacaine inhibited the growth of both breast tumor cell lines in a dose- and time-dependent manner (all $p < 0.001$)
Ecimovic, et al. 2013 [29]	Experimental	MCF7 ER(+) and MDA-MB-231 ER(-) breast cancer cells	With and without sevoflurane	Sevoflurane increased proliferation in MCF7 cells and MDA-MB-231 cells ($p < 0.05$). Sevoflurane increased migration in both breast cancer cell lines, in MCF7 ($p = 0.04$) and MDA-MB-231
Forget, et al. 2010 [24]	Experimental	Pulmonary metastasis of mammary adenocarcinoma (MADB106) in rats	4 groups of treatment: saline, fentanyl, clonidine, ketamine	Fentanyl was associated with a significant increase in the number of lung metastases ($n = 97 \pm 17$ vs. 31 ± 11 in the saline group, $p < 0.05$)
Gach, et al. 2011 [47]	Experimental	Breast cancer cells	Morphine	attenuation of MMP secretion by opioids was not mediated by opioid receptors but was under the control of nitric oxide system
Gupta, et al. 2002 [19]	Experimental	Breast cancer cells (MCF-7 cells)	Morphine and endomorphin	Clinical use of morphine could potentially be harmful in patients with angiogenesis-dependent cancers.
Huang, et al. 2014 [34]	Experimental	prostate adenocarcinoma PC3 cancer cell line	Two groups: Isoflurane, Propofol	isoflurane should be avoided for use in cancer surgery
Lirk, et al. 2012 [58]	*In vitro*	Breast cancer cell lines BT-20 (ER-negative) and MCF-7 (ER-positive)	lidocaine and procaine	A dose-dependent decrease in DNA methylation in response to lidocaine (1, 0.01, and 0.01 mM) after 72 h ($p < 0.001$, <0.001, and 0.004, respectively)
Loop, et al. 2002 [27]	Experimental	human T-lymphocytes	etomidate, fentanyl, ketamine, methohexital, midazolam, morphine, Propofol, thiopental	suppressive effect of the sulfated analogs on neutrophil function is 10- to 100-fold stronger
Lucchinetti, et al. 2012 [55]	*In vitro*	Mesenchymal stem cells from femurs	lidocaine, ropivacaine, and bupivacaine	Antiproliferative effects of ropivacaine on mesenchymal stem cells. Cells exposed to increasing concentrations of ropivacaine showed a dose-dependent reduction in proliferation. ($p < 0.001$)
Luo, et al. 2015 [35]	Experimental	Ovarian cancer (SK-OV3) cells	Isoflurane	Increased expression of VEGF by 56% ($p < 0.05$) and angiopoietin-1 by 62% ($p < 0.05$) after isoflurane exposure. Cell migration was also significantly increased ($p < 0.05$) by five-fold relative to control.
Mammoto, et al. 2002 [59]	*In vitro*	Epithelial cells from patients with Fibrosarcoma (HT1080), Osteosarcoma cells (HOS), malignant melanoma (RPMI-7951)	Lidocaine	Lidocaine inhibited the invasive ability of human cancer (HT1080, HOS, and RPMI-7951) cells at concentrations used in surgical operations (5–20 mM)
Melamed, et al. 2003 [22]	Experimental	Pulmonary metastasis of mammary adenocarcinoma (MADB106) in rats	halothane, diazepam, ketamine+diazepam, Propofol, thiopental	Lung tumor retention is significantly larger in ketamine ($P = 0.23$) and thiopental ($P = 0.056$) groups
Ohta, et al. 2009 [33]	Experimental	bone marrow-derived Dendric Cells (DCs)	ketamine	ketamine inhibits the functional maturation of DCs and interferes with DC induction of Th1 immunity ($p = 0.025$)
Roesslein, et al. 2008 [26]	Experimental	Human $CD3^+$ T-lymphocytes	Thiopental, pentobarbital, etomidate, ketamine, midazolam, or Propofol	Thiopental protects against T-lymphocyte apoptosis
Tegeder, et al. 2003 [46]	experimental	Breast cancer cells	Morphine	morphine signals could be transduced by opioid receptors via a G protein.
Xu, et al. 2014 [14]	Experimental	breast and colon cancer models	COX-2 Blockade	The COX-2/PGE_2 pathway promotes VEGF-independent angiogenesis
Yoon, et al. 2010 [57]	*In vitro*	non-tumorigenic mammary epithelial and breast tumor cells	Lidocaine and Tetracaine	Tetracaine provides a mechanism for the ability to decrease metastatic progression.

PPA: Propofol-Paravertebral Block; GA: General Anaesthesia; NK: Natural Killers; MDA-MB-231: Adenocarcinoma Cell Lines; MMP: Matrix Metalloproteinase; CO-2: Cyclooxygenase-2; Th: T-helper; MOR: μ-Opioid Receptor; NSAID: Non-Steroid Anti-Inflammatory Drugs; IFN-γ: Interferon; VEGF: Vascular Endothelial Growth Factor; PGE_2: Prostaglandin E2;

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NK cell activity, which starts within hours after the operation and can last for days. This effect is related to the severity, duration, and extension of the surgery [12]. The intensity of the peri-operative stress can activate the hypothalamic-pituitary adrenal-axis (HPA-axis) and the sympathetic nervous system (SNS) to produce more catecholamines and prostaglandins, a fact that leads to changes the NK cell activity [2]. In experimental breast cancer models, intraoperative stress could affect tumor development, probably because of catecholamine release, leading to an inhibition of the natural killer T cells function and thus to a decreased resistance to the metastasis procedure [13]. Clinically, it is shown that surgery can decrease circulating NK and T cells through the programmed death-1 (PD-1) and programmed death–ligand 1 (PD-L1) pathway due to the enhancement of PD-1 expression on immune cells [14]. The function of the natural killer T cells may also be reduced peri-operatively due to unintended hypothermia, suggesting that many other factors can influence the resistance of the metastasis and thus the long-term outcome of breast cancer [15].

A wide interest has been raised concerning the role of a naturally occurring lymphocyte sub-population, like the CD4+CD25+ regulatory T cells (Tregs), that are featured by expression of the forked-head transcription factor Foxp3, that has potent immuno-regulatory activity [16]. High intratumoral infiltration by Foxp3+Tregs in breast cancer patients relates to a higher risk of late recurrence [17]. Moreover, an increased concentration of Tregs in the peripheral blood of breast cancer patients has been related to the advanced stage of the disease [18]. Additionally, the Foxp3-related regulatory T-cell activity promotes intratumoral angiogenesis and is linked with pathological features of clinical aggressiveness in breast malignancies [19].

Anesthesia, tumor progression and immune surveillance

Anesthetic agents have complex interactions with cancer cells and immunity, and different classes of anesthetics interact differentially [20]. A direct mutagenic effect has been reported, which may affect the genetic diversity in tumor cells, boosting cancer aggressiveness and metastatic behaviour [21]. Anesthetic and analgesics can also induce proliferation, angiogenesis, and apoptosis [22] and interfere with the immune response in cancer patients after surgery [20]. Chemical mediators such as cyclooxygenase-2 and prostaglandins E2, can be released as a response of the human body to anesthetic drugs, changing the tumor homeostasis and stimulating cancer relapse [23]. They also promote the release of immuno-regulatory factors, such as interleukin 4 [IL-4] and IL-10, transforming growth factor beta (TGF-β), and VEGF, as well as pro-inflammatory cytokines IL-6 and IL-8, which stimulate the tumor angiogenesis and metastasis and have a direct effect on immune surveillance [24,25].

Ketamine and thiopental

Ketamine is a dissociative agent and can be used for induction and maintenance the anesthesia, and also for the treatment of depression and chronic pain. Thiopental is a rapid-onset short-acting barbiturate general anesthetic and nowadays is oft supplanted by Propofol. Both agents have strong immunosuppressive effects. These suppress NK cell cytotoxic activity [23]. Ketamine activates the human lymphocyte apoptosis via the mitochondrial pathway [24] and suppresses the functional maturation of the dendritic cell (DC) [25]. Induction of heat-shock proteins by thiopental has also been reported [26]. Ketamine also reduces the release of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor-α (TNF-α), and thiopental represses the function of the neutrophils and blocks the nuclear factor kappa B (NF-κB) pathway. The NF-κB suppression from thiopental is associated with the inhibition of NF-κB-driven reporter gene activity, blocking T-lymphocyte activation, as well as IL-2, IL-6, IL-8, and IFN-γ expression [27].

Volatile anesthetics

The inhalational agents, such as sevoflurane, isoflurane, and desflurane, are used for induction and maintenance of general anesthesia, they are safe for children and pregnant with a rapid onset and offset. In breast cancer patients undergoing surgery, sevoflurane can increase the levels of pro-tumorigenic cytokines and MMPs [28]. Additionally, it has also been shown that sevoflurane promotes the proliferation, migration, and invasion of Estrogen Receptor (ER)-positive and ER- negative cells [29]. Furthermore, sevoflurane upregulates HIF-1α expression [30]. In an interesting study, serum from breast cancer patients who received anesthesia with sevoflurane combined with an opioid did not suppress breast cancer cell proliferation, in contrast to the inhibition conferred by the serum of patients receiving Propofol combined with paravertebral anaesthesia [31]. In another study, sevoflurane reduced the levels of Polymorphonuclear Cells (PMNs), blocked the release of IL-1β and TNF-α from human Peripheral Blood Mononuclear Cells (PBMCs), and suppressed NK cell cytotoxicity and cytokine-associated NK cell activation [32]. In contrast, studies in patients who received Propofol and sevoflurane-based anesthesia did not observe any effect on NK cells [33].

Isoflurane at concentrations used in clinical practice, similarly to sevoflurane, activates the Hypoxia-Inducible-Factor 1α (HIF-1α) in cancer cells in a dose-dependent manner, promotes its translocation to the nuclei and enhances the transcription of down-stream genes involved in glycolysis, angiogenesis and overall development of an aggressive cancer cell phenotype characterized by increased cellular proliferation, invasiveness, and VEGF expression [34]. This effect is prevented by Propofol, which blocks HIF1α induction by isoflurane, hypoxia, and hypoxia mimetic agents. Moreover, the authors showed that isoflurane promotes resistance of cancer cells to docetaxel chemotherapy. In a relevant study, isoflurane enhanced the malignant potential of ovarian cancer cells through the upregulation of Insulin-like Growth Factor (IGF)-1 and its receptor IGF-1R, as well as of VEGF, angiopoietin-1, MMP-2 and MMP-9 [35].

Overall, Volatile Anesthetics (VA) can affect the function of neutrophils, macrophages, and natural killer cells due to

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a combined effect on multiple targets. VAs target receptors on NK cells preventing adhesion to cancer cells and blocking the degranulation of lytic enzymes preventing NK-mediated cytotoxicity. Similar effects of VA on macrophages have been reported, as these block the secretion of TNFα and phagocytosis. VA can also target calcium channels in neutrophils repressing their activation [36]. T cell proliferation can also be inhibited by Vas [37]. A retrospective study suggested that VA used for surgery of cancer patients was linked with 1.5-fold higher disease-related death events compared to intravenous anesthetics [38].

Opioids

Opioids are drugs that have medically been used for pain relief, including anesthesia. Opioids work by binding to opioid receptors in the central and peripheral nervous system and the gastrointestinal tract. The opiates included morphine, and other semi-synthetic and synthetic opiates such as hydrocodone, oxycodone, and fentanyl. The commonly used in anesthesia opioid drugs may also affect cancer progression through modulation of cell proliferation and death pathways [39]. Although morphine plays an important role in the management of cancer pain, μ-Opioid Receptor (MOR) is associated with tumor progression in some cancer types; thus, it could get involved in metastasis and tumor relapse depending on the tumor type [40]. Opioids also induce the proliferation of endothelial cells and angiogenesis through MAP-kinase activation [41]. Morphine, in clinically applied doses, enhances tumor neovascularization and cancer growth [39,42]. Overexpression of the MOR, which boosts tumor growth and metastasis, is detected in several human cancers [43].

A transnational study of > 2,000 women with breast cancer suggested that a single gene polymorphism of the MOR gene (A118G) is associated with increased survival after ten years in breast cancer patients [44]. However, in another study, it was reported that MOR expression was increased in the tumors of patients who underwent operation with opioid general anesthesia compared with those who had received general anesthesia with Propofol and paravertebral block, but there was no significant influence on the expression of immune cell markers [45].

Morphine also induces p53 phosphorylation and stabilization in breast cancer cells expressing wild-type p53 and causes increased production of p53-dependent proteins, including p21, Bax, and Fas [46]. These records indicate that morphine may delay the development of specific cancers by activating p53. Furthermore, it is suggested that morphine can suspend the expression and secretion of MMP-2 and MMP-9 in breast cancer cells in a time- and concentration-related way [47].

Opioid agents may also reduce the natural and adaptive immune response by binding to expressed opioid receptors on immune cells. Morphine is a classic μ-receptor agonist, and T-cells express these receptors. Morphine has been shown to induce secretion of the anti-inflammatory IL-4 by T-cells [48]. Chronic morphine administration has been correlated with increased levels of regulatory T-cells in the blood of experimental animals [49]. B-cells also express opioid receptors. The activity of morphine on NK cells is complex, as low doses seem to activate NKs, while high doses block their cytotoxic activity [50]. Concerning macrophages, morphine suppresses their phagocytic potential by activating μ- and δ2-receptors [51]. Finally, dendritic cells also express different opioid receptors, and morphine can have divergent effects on their function [52].

In a study, the levels of CD4+cells and the CD4+/CD8+ ratio in breast cancer patients who underwent modified radical mastectomy under remifentanil combined with dexmedetomidine anesthesia were significantly higher than the ones recorded in a control group treated with remifentanil alone. The levels of CD8+ cells were lower one hour after the beginning of the operation and 24 hours after the operation, suggesting that dexmedetomidine can reduce the immunosuppressive effects of remifentanil [53]. Furthermore, Gong et al. showed that the use of opioids in anesthesia could induce immunosuppression by increasing the ratio of CD4+ CD25+Foxp3+ Tregs (T-regulatory cells) population, suggesting that the opioid agents should be avoided in patients with malignancies. Additionally, they found no specific effects of the sufentanil in comparison with fentanyl anesthesia on Treg-counts and Foxp3 mRNA expressions during surgery, although sufentanil had a stronger effect in the increase of the amount of Tregs [11].

In a more recent study was found that the intraoperative use of opioids is associated with improved recurrence-free survival in patients with triple-negative breast cancer, suggesting that opioids may have a controversial effect on different types of breast cancer; thus, more studies in this field are required [54].

Local anaesthetics

Local anesthetics can be used to prevent and/or treat acute pain and chronic pain and as a supplement to general anesthesia. They are categorized as low, medium, and high according to their duration of action and potency. Local anesthetics block Voltage-Gated Sodium Transmembrane Channels (VGSC). VGSCs are highly expressed and active in breast, colon, and lung cancers and are involved in tumor growth control. In particular, lidocaine, ropivacaine, and bupivacaine have an anti-proliferation and anti-differentiation effect and are cytotoxic against mesenchymal stem cells (MSCs) in *in vitro* studies [55]. Chang et al. suggested that the use of lidocaine and bupivacaine in clinically relevant doses can lead to apoptosis of breast cancer cells *in vitro* and *vivo* [56]. Lidocaine and tetracaine, which both inhibit kinesin motor proteins, reduce the formation and function of tubulin micro-tentacles; thus, these drugs may have an unnoticed so far capacity to decrease metastatic spread in breast cancer cells [57]. The use of lidocaine in clinically applied doses promotes DNA- demethylation in ER-positive and ER-negative breast cancer cells in *in vitro* studies [58]. Additionally, lidocaine blocks invasion of the cancer cells by modulating intracellular Ca2+ concentrations and inhibiting ectodomain shedding of

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heparin-binding epidermal growth factor from cell membranes [59]. Furthermore, lidocaine, ropivacaine, and bupivacaine reduce MSC proliferation by causing cell cycle delay or arrest at the G0/1-S phase [53]. However, it could not be determined whether the observed reduction of the T cell concentration was due to decreased IFN-γ, increased cortisol, impaired antigen presentation, surgical stress, or a combination of all these factors.

Moreover, O'Riain et al. found that the combination of general anesthesia with paravertebral anesthesia can lead to the reduction of surgical stress during mastectomy and provide the most favorable postsurgical pain management in comparison with the general anesthesia itself. Moreover, they found no increase in the postoperative concentration of the VEGF and Prostaglandin E2 (PGE2) [60]. A retrospective study of breast cancer patients who underwent surgery demonstrated that the incidence of the recurrence of the disease depends on the type of anesthesia, and it seems to be less frequent in patients who have received a combination of a general anesthetic with the paravertebral block in comparison to patients receiving a combined general with opiate analgesia [61].

Buckley et al. observed decreased IL-10 expression in NK cells in the serum of patients who underwent breast surgery under general anaesthesia [62]. IL-10 is produced by Type 2 helper T cells and is involved in the inhibition of pro-inflammatory cytokines and the down-regulation of cell-mediated tumor immunity [63]. In addition, IL-10 inhibits tumor metastasis through an NK-dependent mechanism [28]. Of interest, an increase of IL-10 levels in the serum of patients with ovarian cancer undergoing surgery with the use of regional anesthetic techniques was found [64].

An interesting study by Desmond et al. evaluated the effects of anesthesia on the infiltration of immune cells in breast cancer tissue in patients with primary breast cancer. Paravertebral regional anesthesia combined with Propofol led to an increase in the infiltration of breast cancer tissue by NK cells and T helper cells [65].

Discussion

In conclusion, currently available preclinical and clinical studies suggest that anaesthetic-induced immunosuppression may promote cancer recurrence in patients with certain types of cancer. Volatile anesthetics promote immunosuppression and boost inflammatory cascade activation. Opioids might enhance cancer relapse and metastasis. *In vitro* and *in vivo* studies demonstrated that local anesthetics inhibit the proliferation and migration of cancer cells and induce apoptosis [66]. Nevertheless, regional anesthesia and Propofol-based anesthesia seem to reduce surgical stress, peri-operative immunosuppression, and angiogenesis compared to general anesthesia with volatile anesthetics and opioids.

Briefly, it is suggested that the peri-operative management of cancer patients should focus on the reduction of surgical stress, the minimization of the use of opioids, and the adoption of regional anesthetics. This could have an impact on anti-tumour immunity and the outcome of cancer patients [67].

Conclusion

The overall experience suggests that the peri-operative period and management of cancer patients is critical in primary cancer therapy and prognosis, thus, it should focus on the reduction of surgical stress, the minimization of the use of opioids, and the adoption of regional anesthetics. This could have an impact on anti-tumour immunity and the outcome of cancer patients.

Authors` contributions

All authors contributed equally to the manuscript and read and approved the final version of the manuscript. All authors read and approved the final version of the manuscript.

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