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The Influence of Peri-operative Factors on Post Surgical Breast Cancer Recurrence

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Abstract

Purpose of review: Although there are various treatment options for breast cancer, control of advanced disease often depends on surgical removal of the primary tumor. Unfortunately, both clinical and experimental studies have shown that cancer surgery may increase the risk of metastases and recurrence. This review examines the evidence for recent developments in perioperative factor and perioperativ intervention that is of relevance to postoperative breast cancer recurrence.

Recent findings: Recently, a study has demonstrated the role of mechanical ventilation in promoting lung metastasis. These observations indicate that the metastasis enhancing effect of mechanical ventilation during general anesthesia should be considered, which may provide novel strategies per-operation to prevent postoperative cancer metastasis.

Summary: Proof of the utility and validity for reducing risk of breast cancer recurrence through advances in preoperative interventions is still evolving. Evidence-based developments in this field are likely to benefit patient's surgical outcomes.

Keywords: Breast cancer recurrence; Perioperative factor; Anesthesia; Hypothalamic-pituitary-adrenal axis; Immunodulation; Stress response; Breast cancer metastasis; Mechanical ventilation; Anti-steriodal antiinflammatory drugs

Abbreviations: MV: Mechanical Ventilation; 4T1 cells: Mouse Mammary Carcinoma Cell Line; EpCAM: Epithelial Cell Adhesion Molecule; TNFα: Tumor Necrosis Factor Alpha; VEGF: Vascular Endothelial Growth Factor

Introduction

The main cause of high breast cancer mortality rates is the development of distant metastasis. The molecular mechanisms controlling metastatic growth and dormancy continues to provide many challenges, despite advances in the understanding of its pathogenesis [1,3]. Surgical resection of the primary tumor is the mainstay of treatment; however, both clinical and experimental studies have shown that cancer surgery may increase the risk of metastases and recurrence [2,3]. Metastasis is a complex coordinated process that depends on the interaction between cancer cells and the tumor micro-environment, involving several cell types, cytokines, and cell adhering molecular pathway [4].

During metastasis, cells that are arrested in a capillary bed (intravasation) are able to invade the host organ parenchyma (extravasation), resulting in the growth of secondary tumor cell colonies [5]. There are many perioperative factors that impact on the risk of metastases, such as, tumor cell dissemination into bloodstream by surgical manipulation, removing the source of angiogenesis inhibitors by surgical removal of primary tumor, secretion of immunosuppressive agents, stimulation of inhibitory pathways by surgical stress, anesthetic medication, anesthetic technique (such as, mechanical ventilation during general anesthesia) and other per operative factors [3]. All these perioperative factors offer a favorable microenvironment, promoting residual and circulating cancer cells to proliferate and metastasize after operation [2]. Undergoing surgery thus creates the "perfect storm" [6], throughout which the judicious and careful selection of perioperative intervention is vital for reducing the racial disparities in breast cancer survival. This review collates the evidence regarding anesthetic effects on metastasis and recurrence of cancer.

Effect of Surgery Per Se on the Progression of Breast Cancer

Tumor manipulation during surgery may increase the metastatic process via tumor cell dissemination into the lymphatic and bloodstreams resulting in the seeding of tumor cells in distant organ [7]. Tumor cells require a favorable microenvironment to survive and proliferate at distant sites. Moreover, many patients shelter micrometastases and scattered tumor cells in distant organ at the time of surgery [3]. Pre-existing micro metastses may grow out as a result of

decreased levels of anti-angiogenic factor and increased levels of growth factors and factors related to tumor vascularity [3,5]. Specific factors initiated by surgical trauma can influence the progression of cancer, including catecholamines, prostaglandins, glucocorticoids, various cytokines, pro-angiogenic factors, opioids, etc. [8]. Growth factors such as vascular endothelial growth factor (VEGF) and EGF, elevated by surgery, are demonstrated to potentiate the metastatic ability of cancer stem cells [9].

Cell-mediated immunity has shown anti-metastatic activity in animals and humans. There is an association between stress-induced attenuation of NK cell activity and the promotion of breast tumour growth and metastasis in a rat model and patients with low levels of NK cells and increased risk of developing cancer, or metastases after cancer surgery [10]. Surgery and the stress response have been shown to suppress cell-mediated immunity, NK cell activity in particular, in experimental and clinical studies. Following a breast surgery cellular immunity remains suppressed for several days with decrease in immunostimulating cytokines (IL-2, IL-12, and interferon (IFN)-γ) and increase in production of anti-inflammatory cytokines. Circulating levels of NK cells, dendritic cells, CTLs, and T-helper cells also decrease [11]. The stress response to surgery includes a number of hormonal changes initiated by neuronal activation of the Hypothalamo-Pituitary-Adrenal (HPA) axis. Surgery is one of the most potent activators of ACTH and cortisol secretion, and increased plasma concentrations of both hormones can be measured few minutes after the start of surgery [12]. The resultant stress response is characterized by the release of catecholamines and prostaglandins. Many studies have particularly reported on the enhancement of catecholamines and prostaglandins on cancer development, both by immunosuppression and by direct facilitation of malignant tissue progression [8]. The inflammatory mediators induced by pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) [13], which are known to increase the activity of cyclooxygenase-2 (COX-2). A highly poent inflammatory enzyme, COX-2 plays a pivotal role in promoting cancer growth and metastasis. The perioperative interventions to decrease the levels of these factors for a better prognosis have been taken on in clinical studies. Perioperative use of beta blockers and COX-2 inhibitors reduced lung tumour retention (LTR) and restored NK cell function in a rat model [14].

Effect of Anesthesia on Cancer Volatile Agents During General Anaesthesia

In a recent retrospective study, it was found that cancer patients had a worse survival outcome if they received inhalational anesthesia [15]. Isoflurane and halothane can attenuate NK cell cytotoxicity by IFN therapy. It was reported that isoflurane could promote the growth and migration of glioblastoma cells [16], up-regulate levels of hypoxia-inducible factor (HIF)-1α and HIF-2α and intensified expression of VEGF A [17]. Inhalational anesthesia inhibits the immune system by decreasing the function of natural killer cells, which play an important role in protecting against proliferation of cancer cells [18].

Mechanical Ventilation During General Anaesthesia

Huang et al. [18], using a mouse model, demonstrated that mechanical ventilation promoted lung metastasis. Mechanical ventilation promotes tumor establishment by attracting circulating 4T1 cells to the site of local inflammation and tissue within lung damage induced by mechanical ventilation. Moreover, demonstrated increased infiltration of macrophages within the metastatic tumor and increased EpCAM expression in lung metastases and surrounding lung tissues after mechanical ventilation. These observations indicate that the metastasis enhancing effect of MV should be considered, which may provide novel strategies per-operation to prevent postoperative cancer metastasis [19].

Local and Regional Anesthesia

Regional anaesthesia moderates the neuroendocrine stree response to surgery by block afferent neural

transmission from the central nervous system and activating the stress response, and by blocking descending effect activation of the sympathetic nervous system. Paravertebral anesthesia is a regional anaesthesia technique that is suitable for breast surgery when applied in the upper thoracic region and has been shown its efficacy in suppressing the stress response to breast surgery. In a retrospective analysis of existing medical records [20,21]. Perez-Gonzalez O et al. compared local recurrence and metastases in patients who had breast cancer surgery with and without paravertebral analgesia and observed a substantial reduction in tumor recurrence and metastases when breast cancer surgery was performed with paravertebral anesthesia and analgesia. The authors suggest that regional anaesthesia and analgesia thus might help to maintain perioperative immune function both by reducing general anesthesia requirements and by sparing postoperative opioids. To the extent that paravertebral anesthesia and analgesia help to maintain normal perioperative immune function, the technique seems likely to reduce the risk of tumor recurrence or metastasis [22]. Lidocaine has a protective effect against breast cancer cells in experimental studies. The anti-tumor properties of local anaesthetics offer a potential opportunity for clinical application. Intravenous use of lidocaine has been shown to possess an anti-inflammatory property [23].

Effect of Intravenous anesthetic agents

Beta receptor antagonists

The sympathetic nervous system has been implicated in mediating stress-induced alterations in NK cell activity; particularly through stimulation of beta-adrenergic receptors Peripheral β-adrenergic stimulation can suppress NK cell function [24]. Use of perioperative β blockade has been shown to halve the metastasis rate in animal model [25]. Hypertensive

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patients on chronic beta blockade were shown to have reduced rates of cancer recurrence, distant metastasis and a longer disease free interval. Other possible mechanisms might be a reduction in VEGF secretion and surgical stress response [24,25].

Propofol

Propofol is considered a 'safer drug' in oncoanesthesia owing to its predominant antitumor effects via inhibition of Cycloxygenase (COX)-2 and Prostaglandin (PG) E2. Propofol exerts anesthesia by activating GABA A receptors directly, to slow the channel-closing time and by blocking sodium channels [26]. Propofol is supposed to protect the immune system from being inhibited perioperatively and have a lower inflammatory response than volatile agents [26,27]. Thus, the author's retrospectively examined the link between propofol-based total intravenous anesthesia (TIVA) and recurrence or overall survival in patients undergoing modified radical mastectomy (MRM) and demonstrated that propofol-based total intravenous anesthesia (TIVA) for breast cancer surgery can reduce the risk of recurrence during the initial 5 years after modified radical mastectomy [28].

Opioids

Opioid administration has been shown to suppress immune system by diminishing NK cell activity. The suppression is naloxone reversible. Page et al. [29] while evaluating the duration of opioid exposure on tumor promotion in an animal model, observed that perioperative, especially preoperative administration of morphine has a favorable effect on tumor free survival. Gupta found that Morphine increased angiogenesis and stimulated the growth of breast cancer i mice. Patients with concomitant regional anesthesia might require less general anesthesia and thus perhaps have less anesthetic-induce immune impairment. But the major effect of regional analgesia is to spare patients perioperative opioids [30].

Other Agents

Ketamine attenuates production of the pro-inflammatory cytokines, IL-6, and TNFα and suppresses NK cell function by peripheral b-adrenergic stimulation [31]. Ketamine attenuates production of the pro-inflammatory cytokines, IL-6, and TNFα and suppresses NK cell function by peripheral b-adrenergic stimulation [31]. In a model of breast cancer metastasis, rats were anesthetized for 1 h with ketamine, thiopental, halothane, or propofol, and then injected IV with MADB106 tumor cells [18]. The number and activity of circulating NK cells after anesthesia and lung tumor retention 24h later was assessed. Lung metastases were counted 3 weeks later. The author found ketamine caused a significant decrease in NK cells, and increased lung tumor retention and lung metastases most potently. Even as low a dose as 0.08mg/kg of midazolam can inhibit lipopolysaccharide-induced production of IL- 1β, TNFα, and IL-6 and 8 by monocytes [32].

Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

Inflammation plays an important role in cancer. Long-term administration of NSAIDs has shown to decrease the incidence, recurrence and proliferation of various cancers, such as colon and breast [33]. But only a few studies have focused on the effect of perioperative use of NSAIDs. A retrospective study indicated that perioperative intravenous administration of ketorolac for breast cancer patients was marginally associated with better overall survival (P = 0.05) [34]. Ketorolac given before surgery was also found to have a lower cancer recurrence rate [35,36].

Conclusion

A growing body of evidence has revealed that cancer surgery can increase the risk of metastasis. Thus, the

perioperative period is critical in determining the risk for post-operative metastatic disease, and offers a window of therapeutic opportunity against residual malignant disease. There are many perioperative factors that impact on the risk of metastases, such as, tumor cell dissemination into bloodstream by surgical manipulation, removing the source of angiogenesis inhibitors by surgical removal of primary tumor, secretion of immunosuppressive agents, stimulation of inhibitory pathways by surgical stress, anesthetic medication, anesthetic technique (such as, mechanical ventilation during general anaesthesia) and other perioperative factors. However, it is impossible to separate the individual effects of anesthesia, surgery, and other perioperative interventions on the immune response [37]. Therefore, a thorough knowledge of tumor oncogenesis, stress response and factors in perioperative microenvironement is essential for the development of perioperative therapeutic interventions to limit the post surgical breast cancer recurrence.

Conflict of Interest

There exists no conflict of interest.

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