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# Perioperative Period is a Critical Gap for Minimal Residual Cancer Cells Progression and Therapy: Biological and Molecular Based Evidences

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**Abstract**

Although surgery is the main treatment for solid tumors, it could enhance the growth and metastasis of minimal residual cancer. In this review article we have discussed the perioperative changes in cancer cells and surrounding environment as well as the alterations in the immune system. Several trials are ongoing to develop new diagnostic and therapeutic options for minimal residual cancer after surgery.

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## Introduction

Surgery is the first-line treatment for patients with solid organ tumors. However, even with complete resection of the tumors with clear safety margin, large number of patients harbors minimal residual cancer cells and ultimately dies of tumor recurrence [1].

It has been demonstrated using different animal and tumor models that surgery could enhance the growth of residual cancer and the formation of metastatic disease [2–11]. Moreover, the number of metastatic deposits is directly proportional to the magnitude of surgical stress [6, 12]. In clinical research reports, a complicated postoperative course may be associated with reduced cancer survival and increased incidence of metastases [13, 14]. It has been suggested that the adverse impact of surgical stress on the body's innate tumor defense mechanisms and inadvertent seeding of tumor cells during surgical procedures, local and systemic release of growth factors such as vascular endothelial growth factor (VEGF) and other cytokines and development of chemo- resistance and apoptosis resistance may explain how the surgical procedure itself could promote cancer recurrence after excision [6, 15-22]. There is also growing interesting evidences on the impact of anesthesia on the outcome of cancer surgery. In this review article we have selectively reviewed the literature to evaluate the perioperative changes in cancer cells and surrounding environment so that new therapeutic options can develop for minimal residual cancer after surgery.

## Methods

The literature in this review was obtained from a search that was confined to pubmed& database and Google scholar up until August, 2018. Results were restricted to the English language. Search terms included 'tumor metastases and surgical stress', 'perioperative period and natural killer cells', 'IV anesthetic drugs and cancer', 'volatile anesthetic drugs and cancer', 'opiates and cancer', 'local anesthetic drugs and cancer', 'regional anesthesia and cancer', 'epidural anesthesia and cancer', and 'perioperative blood transfusion and cancer recurrence'. Relevant references from the articles identified in the literature review were also obtained, and all primary sources were retrieved. About one hundred and seventy articles, published from April 1980 to August 2018, including studies in vitro, animal models, and clinical trials, have been considered. After a careful screening process, 128 articles were considered eligible and reviewed for quality. The screening process took into account factors such as language, publication data, availability of an abstract and full text, relevance, and study type.

## Minimal Residual Cancer

Minimal residual disease is the term used to describe the tumor cells that remain after curative resection. These can be microscopic deposits at the surgical margins or micro-metastases [23]. Studies in humans have demonstrated that surgery itself can promote the development of metastases, for instance by inhibiting NK cell activity [24]. Therefore, the perioperative period supposed to be a critical time in the life of the residual cancer cells post-resection. Even with frozen section confirmed clear margins, 'minimal residual disease' remains due to intraoperative embolization of tumor cells into surrounding tissues [23]. Preexisting 'micro-metastasis' also is a concern following resection of the primary tumor. Whether the extruded cancer cells left in the body will lead to an attack depends on the tumor microenvironment during the perioperative period. It has been observed that presence of cancer cells in the circulation beyond 24 h following surgical resection of primary tumor is an independent predictor of increased tumor recurrence [25]. Theories based on available data suggest alterations in antigen presentation; secretion of immunosuppressive agents; secretion of growth factors required for wound healing and stimulation of inhibitory pathways by surgical stress, anesthetic medication, and other perioperative factors all are involved in tumor recurrence [21, 22, 26]. This can lead an otherwise occult residual minimal disease towards 'immune escape' and regrow to a full cancer. Therefore, controlling the immunosuppressive effects of perioperative physiology and maximizing host immunity for preventing cancer relapse should be a part of our strategy in cancer management.

## The Critical Perioperative Period

The immediate postoperative period is a uniquely susceptible time for the formation of metastases due to alteration of multiple factors that act

upon minimal residual cancer cells. One of the key mechanisms responsible for the pro-metastatic effects of surgery is postoperative dysfunction of innate immune system mainly the Natural Killer (NK) cells [2, 3, 27]. Other mechanisms is the change in the microenvironment of the cancer cells as well as the expression of growth factors which are necessary for wound healing and at the same time enhance tumor growth and metastasis, finally the development of apoptosis resistance.

It has been found that immunosuppression response in the postoperative period is due to the effect of neuroendocrine system, inflammatory process and hypothalamic-pituitary adrenal axis [28]. Psychophysical stress has been suggested to be a predisposing factor for cancer development [29]; therefor, during the perioperative period, levels of stress markers as epinephrine and norepinephrine are markedly raised. These neurotransmitters are involved in the body's response to surgery and could be responsible for the association between stress and cancer progression [28, 30]. It has been noticed that cancer cells express adrenergic receptors type 1 and type 2, thus epinephrine and norepinephrine could activate intracellular events which control number of molecular pathways that determine cancer cell behavior as malignancy and invasiveness. Depending upon these findings and other findings, synthesis of cancer therapies specifically addressing the pro-metastatic changes that may happen immediately following cancer surgery could be a revolution in cancer management. Therefor, perioperative period represents a therapeutic window of opportunity to interfere with the metastatic process. While traditional cancer therapies such as cytotoxic chemotherapy are considered too toxic to be administered to patients recovering from major surgery, the early postoperative period may be an ideal period for immune-based anticancer therapies because the tumor is at its absolute lowest burden just following the surgical removal of the primary tumor [31].

**Tumor Microenvironment**

It has been assumed that recurrent tumors arise from transformed neoplastic clones that are more resistant to chemotherapy, immunotherapy, and radiation [32]. We and others believe that primary and recurrent tumors of equal size have fundamentally different microenvironments that explain their different response to therapies.

*Tumor Microenvironment and Cancer Vaccines*

Cancer vaccines have been proposed to treat patients after surgery to prevent relapses by augmenting endogenous antitumor immune responses [33, 34]. This strategy may have potential benefits such as low toxicity, tumor specificity, and long-lasting immunity. Most importantly, cancer vaccines are maximally effective for limited disease burden; thus postoperative administration looks appealing because of the presence of minimal residual disease [32, 34-36]. Cancer vaccines have been evaluated with encouraging results in hundreds of preclinical studies in animal models with small amounts of primary tumor burden [32, 37-40]. Unfortunately, several clinical trials have been conducted for evaluation of cancer vaccines and some of them used antigen-specific effector T lymphocytes aiming at recurrence prevention in patients after surgery. However, the responses have been infrequent. [33, 34] [40-43]. We assume that primary and post resection residual tumors have essential biological and micro-environmental differences which extend to the recurrent tumor. This may explain the variation in response of the primary and recurrent tumor to cancer vaccines as cancer vaccines may inhibit a primary low burden tumor but may fail to supress a recurrent tumor. It has been observed that recurrent tumors have an immunosuppressive environment rich in regulatory T cells (T-regs), pro-tumor cytokines that inhibit cytotoxic CD8 T lymphocytes and expanded populations of tumor-associated macrophages (TAMs). In contrast, small primary tumors had normal antitumor effector CD8 T lymphocytes. Moreover, in animal experiments, recurrent tumors found to be refractory to many cancer vaccines that could eliminate primary tumors. Interfering with these immunosuppressive pathways results in restoring the efficacy of tumor vaccine in recurrent tumors [44].

**Immunity and cancer**

*Response of an Intact Cellular Immune System to the Presence of Tumor Cells*

The host defense against the development of cancer recurrence requires intact cellular immune

system [29]. In this regard, Natural killer (NK) cells which are a subpopulation of large granular lymphocytes are the primary defense against cancer cells [45]. These NK could spontaneously recognize and lyse tumor cells. Unfortunately, many studies show that surgery could suppress NK cell activity leading to the development of metastatic disease. Moreover, patients with a low level of NK cell activity may have a higher incidence of cancer recurrence [46]. Animal studies have shown that stress-induced reduction in NK cell activity can induce carcinogenesis and tumor development that can be restored by Interleukin-2 (IL-2) and interferon-g (IFN-g) [24, 47].

Cytotoxic T-cell function has been demonstrated to be another vital immune element. For instance, it has been found that high cytotoxicity against primary localized lung cancer could result in development of complete remission at 5 years. Other immune cells like dendritic and cells mononuclear cells also have anti-metastatic activity [48].

Immunosuppressive therapy which is necessary in solid-organ transplant recipient appears to promote the development of metastases. This may highlight the significance of an intact cellular immune system [49]. It has been found that, tumor cells from metastases in immune-competent mice have genetic alterations enable them from invading host immunity, while tumor cells from metastases in immune-compromised mice lack these genetic changes [50]. While cell-mediated immunity may not eradicate the primary tumor; it may eliminate minimal residual disease. This concept may emphasize the critical role of surgery for the primary tumor. Many patients have residual cancer cells in sites such as lung and bone marrow but do not progress to overt metastases [51].

Unfortunately, there is a perioperative immunosuppression that envolves the cellular immune system. This is a result of the neuroendocrine and cytokine stress response to surgery and various anesthetic techniques as well as other perioperative factors as we will detail below [52].

*The Effect of Surgery on Host Defense Mechanisms and Metastatic Development*

Surgical excision is the main step in treatment for solid tumors. 'however, surgery itself can promote the development of metastases, for instance, by inhibiting NK cell activity and growth facilitation of pre-existing micro-metastases. The potential mechanisms that may induce tumor growth and metastasis after surgery have been shown below.

i) Tumor manipulation and shedding during surgery may release tumor cells into the circulation. Using polymerase chain reaction (PCR) can detect tumor cells in patient blood, which shows increase in their number after surgery [53].

ii) The presence of the primary tumor may itself prevent neovascularization of tumor metastasis, and therefore, tumor removal may eliminate a safeguard against angiogenesis. This may induce survival and growth of minimal residual cancer cells.

iii) Local and systemic release of growth factors during surgery and in the short post-operative period may promote tumor recurrence both locally and at distant sites. EGF and transforming growth factor-b levels are increased, as is VEGF. In addition, anti-angiogenic factors, such as angiostatin and endostatin, may be reduced by surgery which promotes neovascularization [45].

iv) Perioperative immunosuppression that includes the cellular immune system and natural killer cells (NK cells).

Laparoscopy is less immunosuppressive than laparotomy [54]. Laparoscopic resection of colorectal carcinoma has been shown to be associated with a longer disease-free survival and a longer time to recurrence when compared with open resection [55]. Increased surgical stress has been shown to augment cancer metastases in a mouse model [6].

NK cells are cytotoxic lymphocytes of the innate immune system which has a principal role in the control of tumor growth and metastases. Dysfunction of NK cell after surgery has been proved in human patients [2] [56-58] as well as animal experiments [27, 60]. Postoperative NK cell suppression is associated with increased metastases in animal models [27] [59-62]. In laboratory supported clinical studies, low NK cells activity during the perioperative period is associated with a higher rate of cancer recurrence and mortality [63, 64]. The use of recombinant IL-2 and IFN-Î³ in the perioperative period

have been explored in early phase clinical trials which revealed their potential ability in preventing postoperative NK cell suppression and improve progression-free survival [17-20]. Unfortunately, further research in the point has been hindered by tolerability problems of this nonspecific cytokine therapy combined when used in major surgery [31]. NK cells can also be activated by certain viruses. It has been reported that preoperative administration of replicating viruses, such as novel anti-cancer Oncolytic Viruses (OV), and non-replicating viral vaccines, such as influenza vaccine, can suppress surgery- induced NK cell dysfunction and reduce metastatic activity [27, 65-69].

**Anesthetics and Cancer**

There is growing evidences on the effect of anesthesia on the outcome following cancer surgery. Anesthetic agents are powerful pharmacological medications that have diverse and potent impacts on many cellular and organ functions. Essentially, a number of different medications and techniques can be used in combination during anesthesia. There are numerous increasing evidences that different anesthetic drugs and techniques may influence long-term outcome in cancer patients by modulating the neuroendocrine stress response and via its impact on the immune system. Moreover, the potential direct effects of anesthetic drugs on cancer cell biology and molecular processes are also progressively recognized. Although many researches have been produced in this area, the role of anesthetics in cancer progression has not yet been fully investigated nor understood.

Preclinical data suggest that regional anesthesia, in contrast to general anesthesia, could potentially minimize the incidence of metastasis [70, 71]. Generally, inhaled anesthetics can inhibit cancer cell proliferation in a time-dependent manner resulting in late apoptosis of these cells. However, at the same time, they have a negative effect on cytokine release and natural killer cells cytotoxicity [72].

Clinical studies may support the use of some intravenous anesthetics, such as propofol, with the restriction of use of other intravenous anesthetics such as ketamine and thiopental as well as volatile anesthetics. The addition of regional anesthesia might decrease recurrence after cancer surgery [73, 74]. However generally the available clinical data are inconclusive and there is a controversy in these data.

The combination of paravertebral block and general anesthesia in patients had breast cancer surgery was associated with a lower incidence of cancer recurrence and longer disease-free survival [75]. Recently, another study on the effect of combined use of paravertebral block and propofol in surgery for breast cancer, showed a reduction of pro-tumorigenic cytokines as IL- 1 and IL-8, and a rise in IL-10 which has antitumor activity [76].

The association of protocols of total intravenous anesthesia with propofol and synthetic opioids and Loco-regional anesthesia with analgesia seems to reduce perioperative factors that may enhance the growth of minimal residual disease after surgical removal of primary tumor [77-81]. It has been found that levels of IL-6 and TNF alpha were significantly reduced in patients treated with propofol and remifentanil, compared with another group treated with isoflurane. This may suggest that propofol and remifentanil may have the potential to suppress the inflammatory response to surgical stress greater than inhaled anesthetic protocol that use isoflurane [78].

In patients underwent radical prostatectomy, the cancer recurrence risk was 57% lower in those who treated with epidural anesthesia- analgesia when compared to general anesthesia and opioid analgesia [80]. Contrary to this, Tsui et al. have got different conclusions. After five years of follow up, patients who underwent prostatectomy for adenocarcinoma treated with general anesthesia alone have no difference from those who treated with general anesthesia and epidural block in terms of disease-free survival [81].

Further multi center randomized clinical trials are needed to evaluate the effect of different anesthetic drugs and techniques on postsurgical cancer recurrence [80-82].

**Surgical Stress and Chemo-resistance /apoptosis resistance**

*Survivin as Inhipitor of Apotosis: IAP*

Survivin is highly expressed in a wide range of solid tumors and hematological malignancies.

Survivin overexpression may predict the response to chemotherapy and radiotherapy. The system represented by human epidermal receptor (HER2), epidermal growth factor receptor (EGFR) and survivin interferes with the chemotherapeutic drugs that depend on apoptosis in their action [83, 84]. In an experimental animal model, we have shown previously that the expression of EGFR, HER2, and surviving increased after surgical stress. However the increase was lower after CO2 pneumoperitoneum than after laparotomy. This may affect the chemo-sensitivity of the minimal residual cancers or metastasis following surgery, supporting the role of minimally invasive surgery for cancer [22].

Studies on survivin have shown that survivin suppression can induce apoptosis of tumor cells. Moreover, it can enhance sensitivity to apoptosis induced by existing anticancer drugs and other apoptotic stimuli. YM155 is a novel survivin suppressant. YM155 inhibited the growth of 119 human cancer cell lines, with the greatest activity in lines derived from non-Hodgkin's lymphoma, hormone-refractory prostate cancer, ovarian cancer, sarcoma, non-small-cell lung cancer, breast cancer, leukemia and melanoma. It was found that the anti-survivin effect of the small molecule inhibitor YM155 in renal cell carcinoma cells is mediated by inhibition of the NF-κB pathway in a time dependant manner. Other new experimental agents supposed to antagonize survivin are under research [85, 86].

**Tracing Minimal Residual Cancer**

CTC are defined as Circulating Tumor Cells in the blood stream that may originate from the primary tumor or distant metastases. These cells could be found in the tumor draining venous system, the peripheral blood, the central venous blood and the portal venous system or even within the arterial blood circulation. It has been estimated that approximately $10^6$ cells per gram of primary tumor are shed into the systemic circulation every day [87]. However, most of these cells will die in the bloodstream by apoptotic cell death or shearing forces so ultimately they will not be able to grow as distant metastases. Animal studies have shown that less than 0.1% of tumor cells released into the circulation have the ability to form distant metastases [88].

When these CTC settle down in the bone marrow, they form Dormant Tumor Cells (DTC) that act as a reservoir and remain there in dormant states until will be reactivated to enter the blood-stream once more [89, 90]. Tumor manipulation during surgery, colonoscopy or similar procedures has the potential of CTC releasing [91-94]. CTC can also be present as tumor micro-emboli or cell clusters [95].

DTC are thought to act as a key factor in late disease recurrence. Even after several years of dormancy, dormant tumor cells in the bone marrow can eventually be reactivated [96, 97]. When DTC present in lymph nodes they are known as isolated tumor cells (ITC). Both micro-metastases and ITC in lymph nodes can be detected by using molecular biology techniques such as staining with tumor specific antibodies or FACS studies of lymph node tissue and reverse-transcriptase polymerase chain reaction (RT-PCR). Conventional hematoxylin and eosin (HE) staining done in the routine pathological study cannot be used for this target [98]. CTC, DTC, ITC and micro-metastases are all considered as minimal residual disease which is a sign for a systemic disease progression. This may have considera-ble impact on disease progression and patient survival in various solid cancers.

*CTC Culture*

Ex-vivo culture of CTCs is very essential in the study of cancer metastasis since it could assist in comprehensive study of metastasis initiating cells [99].

Short-term CTC culture (3–14 days) has been successfully produced in some cancer types, even at early stages [100–102]. This may help in an ex vivo/in vivo testing of functional analysis and therapies of the disease [103]. On the other side, long-term cultures are more difficult and have only been established in cases with advanced metastasis where a large number of CTCs are necessary to be extracted [104-106]. The success in long-term culturing of CTCs could be promising in establishing personalized cancer treatment by testing of therapeutic efficacy using drug screening [103]. This approach may aid in determining the choice of therapeutic regimen beneficial for patients and hence may lead to advancement of personalized oncology and precision medicine [102].

## Minimizing the Impact of Surgical Stress

*Perioperative Immunomodulation*

Although the post-operative period could be a golden time for circulating cancer cells to metastasize and grow, it also could provide a window of opportunity to support or further enhance the immune system minimizing the risk of cancer recurrences [107, 108].

Promising preclinical results [109, 110], have encouraged clinical trials of preoperative non-specific immune stimulation using low-dose recombinant IFN-a [52] or IL-2 [111– 113]. These clinical trials have shown less NK and T cell suppression following surgery. Preoperative low-dose subcutaneous (s.c.) IL-2 was associated with an improved prognosis in a randomized study of patients undergoing resection of colorectal cancer primary tumors [113]. A Phase II trial in120 patients undergoing resection for renal-cell carcinoma has demonstrated a significant improvement in 5-year DFS with preoperative IL-2 (74vs.62%, p = 0.02) [112]. Moreover, in all of these studies, preoperative IL-2 was safe and well tolerated with adverse events limited to pyrexia (Grade I–III). The data are promising and perioperative treatment strategies, aimed at stimulating the cellular immune system warrants further study.

*Onco-Viruses (OV)*

Onco-viruses are attractive agents that could reverse perioperative immune suppression. Onco-viruses can act through multiple mechanisms which may provide many advantages over known cytokine immune stimulants in the postoperative period. OV can produce a more "physiological" immune-stimulation leading to engaging and maturing Dendritic cells (DC), which in turn activates T cells and NK cells.

Moreover, the OV have the ability to selectively replicate inside cancer cells leading to cancer cell death. Because of the surge of growth factors such as VEGF in the postoperative state, it has been suggested that OV could infect and replicate better in the postoperative period, providing a therapeutic advantage for OV at this critical time [114]

*Safety Concerns Regarding Perioperative OV Therapy and Strategies to overcome them*

OV therapy has the potential risk of developing severe postoperative systemic inflammatory reaction. Moreover, the OV have the risk of spreading to members of management team. These concerns act as obstacles hindering the clinical development of OV therapy.

At the same time, it has been suggested that for NK cell-mediated anti-tumor responses, the intact viral particle and cellular recognition, along with viral genomic RNA and proteins are necessary. Recently, it has been found that Non-replicating forms of MG1, including MG1-UV2 min are novel cancer therapies that could be safely administered in the immediate preoperative period to prevent the occurrence of metastatic disease [115].

## Prospect and Conclusion

Severe surgical stress and postoperative complications cause a profuse release of perioperative cytokine, which could enhance tumor growth and metastasis in experimental models [21, 22] Hirari T et al have named this phenomenon as surgical oncotaxis[116]. Excessive corticosteroid release, peripheral vascular coagulopathy, excessive formation of reactive oxygen species and immune suppression have been proposed to be factors behind this process. Activation of Nuclear factor-kappa B (NFkB) could play a key role in this phenomenon [21]. We and others recommend that minimally invasive surgical techniques should be used, and postoperative complications should be avoided whenever possible to lessen the impact of surgical stress. Furthermore, a small preoperative dose of corticosteroid or the use of free radical scavengers in the perioperative period could be considered. Recently, there has been a great deal of interest in omega-3 fatty acid, because it regulates NFkB activation. More researching for anesthetic techniques that could minimize the surgical stress should be considered. In this regard, it may be important to verify further the association between general anesthesia and loco-regional anesthesia and its impact on the outcomes of cancer patients. The introduction of multimodal treatments that diminish surgical stress and its consequences may be as important as chemotherapy for improving the outcome of patients with cancer undergoing surgery [21, 22,115].

Further technical advances for CTC and DTC detection and concurrent utilization of CTC and DTC may result in a real comprehensive integration of CTC

and DCT in the prognostic and therapeutic strategies. Recently, Yoshino T et al has developed a wide-field fluorescence imaging system for rapid CTC detection. Moreover many scientists are introducing nanotechnology and oligonucleotide aptamers as a next-generation technology for the capture and detection of CTC [117-119].

Although immunotherapy is promising, perioperative treatment strategies, aimed at enhancing the cellular immune system and combating the immune-suppressant effect of surgery needs further studies. In this regard, OV are attractive agents that could combat perioperative immune suppression [114, 115].

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