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Regional anaesthesia in cancer surgery: an update

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Abbreviations:
ASA – American Society of Anesthesiologists
CMI – cell-mediated immunity
COX – cyclooxygenase
CWI – continuous wound infiltration
EA – epidural anaesthesia
IL – interleukin
NK – natural killer
PNB – peripheral nerve blocks
TAP – transversus abdominis plane
TNF – tumour necrosis factor

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Abstract

Anaesthetic techniques can influence the cellular immune system and affect long term outcome. Cancer surgery itself and general anaesthetics, especially opioids, suppress immunity and therefore promote metastases. Regional anaesthesia attenuates the immunosuppressive effect of surgery. Local anaesthetics, contrary to opioids, stimulate the activity of natural killer (NK) cells during the perioperative period. All techniques of regional anaesthesia are very useful and applicable in cancer surgery, either for the anaesthesia itself or for the treatment of postoperative pain. The relationship between regional anaesthesia and cancer recurrence is one of the most interesting topics in anaesthesia today, but we must wait the results of prospective trials before definitive conclusions.

INTRODUCTION

Cancer remains a significant cause of morbidity and mortality internationally. It is the second most common cause of death. The likelihood of tumour metastases depends on the balance between the metastatic potential of the tumour and the anti-metastatic host defences. Surgery is the mainstay treatment for solid tumours, but studies on humans have demonstrated that surgery itself can promote the development of metastases. The potential effect of anaesthesia on long-term patient outcome has been increasingly acknowledged *(1)*. The perioperative period is a critical time and the suppression of host defence mechanisms at that time can have deleterious long-term consequences. The perioperative stress response affects the immune system which has been developed to protect us from infection but also from cancer. Therefore, at the same time cancer surgery may initiate migration of cancer cells through the body and supress the defence immune system. The question that arises is how the choice of anaesthetic technique improves ability of body to eliminate cancer cells and upgrade survival.

PERIOPERATIVE IMMUNE RESPONSE AND CANCER

Animal studies indicate that immune response control over the circulation of tumour cells and micrometastasis is carried out mainly through cell-mediated immunity (CMI), which includes cytotoxic T lymphocytes, NK (natural killer) cells, NK-T cells, dendritic cells and macrophages *(2)*. NK cells are important because they can naturally recognise and kill malignant cells. B-adrenergic stimulation, which increases during stress states supresses NK activity and therefore promotes

metastasis *(3).* Human studies show that low perioperative levels of NK activity are associated with an increased cancer related morbidity and mortality *(4, 5).*

Cancer surgery supresses immunity and therefore promotes metastasis. Growth of pre-existing micro metastases and dissemination of malignant cells during postoperative period is facilitated *(6).* Further, surgical stress activates angiogenesis which contributes to neoplastic growth.

ROLE OF ANAESTESIA IN THE PEROPERATIVE IMMUNE RESPONSE AND CANCER

The choice of anaesthetic technique and drugs profoundly influences the immune response and consequently cancer metastasis. Melamed et al. demonstrated in rats that ketamine, thiopental and halothane reduces NK cell activity and increased lung tumour retention or lung metastasis *(7).* Propofol does not affect metastasis, which may be related to its B-adrenergic antagonist properties *(8).* Another study has been looked at propofol conjugates (propofol-docosahex-aenoate and propofol-eicosapentaenoate) as treatment for breast cancer, as they have been shown to inhibit cellular adhesion, migration and apoptosis in breast cancer cells. Effects of inhalation anaesthetics on tumour growth were studied by Brozovic et al. in mice. Their results confirmed the genotoxic and cytotoxic activity of halogenated inhalation anaesthetics on tumour cells *(9).* Isoflurane and halothane inhibit interferon stimulation of NK cell cytotoxicity in mice *(10).* Multiple studies have demonstrated *in vitro* effects that may have some relevance in the cancer setting. For instance, sevoflurane alters the release of cytokines (IL-1β and TNF-α, but not IL-2) by NK and NK-like cells *in vitro (11).* In humans, one large retrospective analysis found that general anaesthesia for excision of primary melanoma was associated with a decrease in the survival rate compared with local anaesthesia. The difference was attributed to use of general anaesthetic agents. General anaesthesia decreases circulating NK cells in patients undergoing elective orthopaedic surgery *(12).* Neutrophil, macrophage, dendritic and T-cell function are also impaired *(13).* Nitrous oxide interferes with DNA, purine and thymidylate synthesis and depressed neutrophil chemotaxis *(14).* Opioid administration has been shown to suppress cell-mediated and humoral immunity. This includes NK cell activity, production of immune-stimulating cytokines, phagocytic activity and antibody production *(13, 15).* Morphine at clinically relevant doses increases angiogenesis and promotes breast tumour growth in mice *(16).* Tramadol, which has noradrenergic and serotonergic activity, stimulates NK cell activity, both in rodents and humans *(17).* The differences between morphine and tramadol have been shown in humans undergoing hysterectomy for uterine carcinoma. T-lymphocyte proliferation was depressed in both groups, but remained depressed only in morphine group. Neither surgery nor morphine affected NK cell activity, whereas tramadol was shown to enhance NK cell activity. Long term outcome was not reported *(18).*

Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis via inhibition of the cyclooxygenase (COX) enzyme. Tumour cells have been shown to secrete prostaglandins, and this may be a mechanism to evade host cell-mediated immunity *(19).*

When we analyse the effects of regional anaesthesia, we can find two major retrospective studies. One showed a 57% reduction in incidence of biochemical cancer recurrence when epidural analgesia was used for open prostatectomy when compared with postoperative opioid analgesia. The other showed a four-fold reduction in the incidence of recurrence or metastasis in patients who received general and paravertebral anaesthesia and analgesia when compared with general anaesthesia and morphine analgesia for breast cancer surgery *(20).* The effect of regional anaesthesia on human breast cancer cells in vitro has also been investigated. Serum from patients who received propofol/ paravertebral anaesthesia was found to inhibit proliferation but not migration of an oestrogen receptor-negative breast cancer cell line when compared with a sevoflurane/ opioid group *(21).*

The potential ability of regional anaesthesia to improve long-term outcome after cancer surgery can be attributed to at least three different mechanisms. First, regional anaesthesia attenuates the immunosuppressive effect of surgery. Secondly, patients who received regional analgesia have lower opioid requirements. Opioids may themselves inhibit cell-mediated immunity and host anti-tumour defences. Finally, when regional anaesthesia is used in addition to general anaesthesia, the amount of general anaesthetic required during surgery is reduced. Further, local anaesthetics contrary to opioids stimulate the activity of NK cells during the perioperative period. Intravenous infusion of lidocaine reduces surgery-induced immune alterations. The long-term clinical implications of these findings are unknown and warrant future investigations *(13).* Acute pain suppressed NK cell activity too. Optimizing postoperative pain management may attenuate the post-surgical inhibition of host anti-tumour defence mechanism, including NK cells.

Postoperative pain therapy may play a very important role in metastasis after cancer surgery. Page et al. demonstrated in rats that the provision of pain relief attenuates the surgery-induced increase in metastatic susceptibility, likely because of reduction in the stress response. They demonstrated that preoperative intrathecal administration of bupivacaine plus morphine and the perioperative systemic administration of fentanyl significantly enhanced the host resistance to surgery-induced increases in lung metastasis. They suggested that the pain-alleviating

effect of these drugs attenuated the surgery-induced promotion of metastasis rather than having direct effect on immunity, tumour cells or other mechanisms *(22).*

Opioids likely play a profoundly negative role. Morphine has been repeatedly shown to promote angiogenesis. It is well established that opioids inhibit cellular and humoral immune function in humans.

Anaesthetic strategies that protect the immune system have been suggested to guard against this effect and may reduce cancer recurrence and improve length of survival. Regional anaesthesia has been shown to minimise immunosuppression via its opioid sparing effect and by reducing the response to surgical stress.

There are many conflicting studies regarding regional anaesthesia and its impact on cancer recurrence. It has been reported that regional anaesthesia decreases some of the risk factors that promote cancer metastasis by attenuating the neuroendocrine stress response to surgery, reducing pain, the need for general anaesthetics, minimizing opioid use and decreasing pro-inflammatory cytokines. The theory is that regional anaesthesia may leave an intact immune system which could potentially decrease cancer recurrence via endogenous removal of tumour cell microemboli. A large analysis of 42 000 patients with colon cancer who underwent colon resection demonstrated that epidural use was associated with 5-year improved overall survival, but not actual cancer recurrence *(23).*

However, more prospective randomised controlled clinical trials are necessary to statistically demonstrate a causal relationship between regional anaesthesia and cancer recurrence. In general, all techniques of regional anaesthesia are very useful and applicable in cancer surgery, either for the anaesthesia itself or for the treatment of postoperative pain. We previously mentioned the benefits of thoracic paravertebral block for breast surgery and its influence on the cancer recurrence. However, this technique has the potential to offer long-lasting pain relief and reduce postoperative nausea, vomiting and chronic pain. Paravertebral block can uniquely eliminate cortical responses to thoracic dermatomes stimulation *(24).*

The results of studies aimed on application of epidural anaesthesia (EA) in large abdominal surgery are controversial. Although EA is theoretically supposed to be a favourable immune-modulating intervention, not all studies show a consistent beneficial effect from EA in colon cancer patients. There is increasing evidence deriving from animal studies thoracic epidural blockade could have an important role in modifying tissue microperfusion and protecting microcirculatory weak units from ischemic damage, regardless of the effect on macro-haemodynamics. Continuous EA is a technique that ensures quality analgesia for surgery in the upper abdomen. Its advantages are reduction of opioid consumption, lower incidence of cardiac and pulmonary complications, shorter duration of postoperative ileus and early mobilisation of patients *(25).* Christopherson et al. found a better overall survival in the first 1.5 post-operative years in 177 colon cancer patients for stage I-II patients with a mean age of 69 years old who received EA. Nevertheless, the type of anaesthesia did not appear to affect long-term survival *(26).* A significant better overall survival was found by Holler et al. The positive impact of this study was the most significant in the high-risk patients (American Society of Anesthesiologists (ASA) score 3-4) *(27).* The Swedish study of Gupta et al. found a reduction in all-cause mortality in rectal cancer patients who received EA *(28).* Contrary, the study of Myles et al. suggested that the use of epidural block in abdominal surgery for cancer is not associated with improved cancer-free survival *(29).* Study of Hiller et al. considered that effective epidural analgesia improves cancer outcomes following gastro-oesophageal cancer surgery in patients with grouped pathological staging *(30).* Continuous EA is a technique that ensures quality analgesia for surgery in the upper abdomen. The advantages of EA are reduced opioid consumption, lower incidence of cardiac and pulmonary complications, and shorter duration of postoperative ileus and early mobilisation of patients. However, there are some limitations in the use of EA in the liver surgery such as postoperative coagulation disorders.

Contrary to EA continuous wound infiltration (CWI) is analgesic technique of application local anaesthetic directly into surgical wound through multi-holed wound catheter placed by surgeon on the end of the surgery. CWI enables reduction in opioid consumption and opioid related side effects, earlier recovery of bowel function and hospital stay. Continuous wound infusion of local anaesthetics has been successfully applied for postoperative pain control in several procedures but, it is underused in thoracic surgery. Fiorelli et al. in their paper concluded that CWI is an effective, easy and safe procedure. It significantly reduces systemic inflammatory markers, pain scores and opioid intake; and accelerates the recovery of respiratory function *(31).*

In ovarian cancer patients intraoperative use of epidural anaesthesia was associated with an increased time to tumour recurrence after surgery *(32).* Quality improvement in colorectal and gynaecological surgery is performing the transversus abdominis plane (TAP) block. Adding TAP block is appropriate tool to improve patient and financial outcomes and to achieve better results of treatment. Keller and colleges analysed results of 200 patients with colorectal carcinoma and concluded that transverses abdominis plane blocks may be an efficient, cost-effective method for improving laparoscopic colorectal surgery *(33).*

Peripheral nerve blocks (PNB) or plexus blocks can be used when pain occurs in the area of one or more periph-

eral nerves. The pain may arise from primary or secondary tumor deposits or be the result of treatment or secondary complications such as pathological fracture or vascular occlusion. PNB are often used to avoid side effects and complications of general anaesthesia, particularly respiratory-related effects, and to provide analgesia while minimizing opioid use. PNB are widely-used for surgical anaesthesia as well as for postoperative pain control, and offer distinct benefits over general or central blocks in certain clinical situations. Further, PNB provide analgesia that may be superior to other techniques for some patients. Koshy et al. described successful continuous femoral block for pain relief of acute severe cancer related pain caused by pathological femur fracture *(34)*. Locoregional anaesthesia provides better pain control, eliminating the need for opioids in the postoperative period and resulting in negative effects on immune function and tumour growth; it also reduces the release of endogenous opioids *(35)*.

CONCLUSION

Finally, we could conclude that the relationship between regional anaesthesia and cancer recurrence is one of the most interesting topics in anaesthesia today. The concept that anaesthesia can influence the outcome of cancer would raise our speciality to a new level. We must wait the results of prospective trials before definitive conclusions.

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