Sri Lankan Journal of Anaesthesiology 20(2): 68 - 72 (2012)

REVIEW ARTICLE

Cancer recurrence, peri-operative interventions and anaesthesia: Review of current evidence

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In recent years, the anaesthesia profession has become increasingly involved in perioperative medicine. This interest has, perhaps, no more appropriate focus than in the field of perioperative interventions that may reduce the risk of cancer recurrence in the surgical oncology patient.
There is strong evidence that in the perioperative patient under acute immune and inflammatory stress, in the setting of minimal residual disease, an acutely high risk of metastasis exists.
This review will focus on some of the more recent animal and human research in this field and aim to provide a glimpse into an area of complex, uncertain and yet encouraging evidence that interventions in the perioperative period could have significant impact on long term cancer outcomes.

Key Words: cancer, anaesthesia, recurrence, relapse, perioperative

Surgical resection remains at the forefront of management for most solid organ tumors including breast, prostate, and gastrointestinal carcinomas. Importantly, cancer recurrence accounts for the majority of deaths in this population[1] as a result of metastasis to distant organs.[2,3] However, surgery itself is also a potent trigger for metastasis[4], an idea that has been known and studied for many years. The possible causes for this include residual minimal disease, dissemination of tumor cells at the time of surgery and the profound alteration and suppression of the body's immune response due to the metabolic, neuro-endocrine, inflammatory and immunological stress.[3] Examples of surgical factors that can promote metastasis at the time of surgery are shown in Table1.

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[1]Vascular Endothelial Growth Factor, [2]Endothelial Growth Factor, [3]Natural Killer

Table 1. Surgical factors that may promote development of metastases.[5]

	Proposed mechanism	**Example**
Handling and disruption of tumour	Release of tumour cells into the circulation	Number of circulating tumour cells shown to be increased after surgery
Decrease in circulating anti-angiogenic factors	Primary tumour may release these factors; removal of the tumour prevents this	Angiostatin and endostatin (both anti-angiogenic) may be secreted by primary tumour
Increase in local and systemic release of growth factors after surgery	Favour growth of metastases	VEGF[1], EGF[2] levels are increased after operation
Perioperative immunosuppression due to surgery	Cellular immune system suppressed for days; loss of tumour surveillance protection	Decrease in number of circulating NK[3] cells cytotoxic T-lymphocytes, dendritic cells, and T-helper cells

There are many factors that impact the potency of a patient's immune system in the perioperative

period. Pain, blood transfusion, hypothermia, hypoxic episodes, organ hypoperfusion, hyperglycaemia as well as direct immunosuppression from anaesthetic agents[6] have all been described.[7] These magnify the preoperative effects of neo-adjuvant chemo-radiation therapy, deconditioning and malnutrition. Furthermore, post-operative chemo-radiotherapy and the increased metabolism required for surgical healing all contribute to prolonged immunosuppression. Compounding this, the neuro-humoral stress response of surgery, particularly in gastrointestinal surgery, is associated with a deleterious shift in the body's immune system towards immunosuppression.[8]

The thrust of current research has been to explore the perioperative role of the anaesthetist in preventing or delaying recurrence of cancer in the face of inevitable 'minimal residual disease' post-operatively. Examining this role requires an understanding of the immune system's response to surgical stress. The body's innate 'immune surveillance' system comprises of three phases: Elimination, Equilibrium and Escape.[7,9] Tumor cells detected by the body that avoid Elimination remain dormant (Equilibrium) or multiply under selection pressure and subsequently 'Escape'. Critically, each of these phases are mitigated intricately by 'anti-cancer' Natural Killer cells, cytotoxic T-lymphocytes, T-Helper cells, inflammatory cytokines, prostaglandins, cytokines and tumor associated macrophages. Controlling the immunosuppressive effects of perioperative physiology and maximising host immunity is likely to be critical in preventing cancer relapse.[10]

Regional Anaesthesia

A review of the current literature regarding the potential for regional anaesthesia techniques to influence the rates or speed of recurrence is dominated by a large number of heterogeneous retrospective analyses.[11-14] The nature of the outcome being explored (over many years) and the speed with which interest in this field has been generated is such that to date, no prospective randomised studies have been published. Hypotheses generated (for the role of perioperative regional or neuraxial blockade in cancer recurrence) center on reduction in associated opioid use[15], obtunding lymphatic drainage [16] and overall reduction in stress response – prevention of immune suppression.[17]

Initial interest in this field was stimulated by animal studies [18,19] and was shown by the increased time to disease free recurrence in patients receiving additional paravertebral blockade compared with general anaesthesia alone for breast cancer surgery.[11,20] Favorable outcomes from the use of perioperative neuraxial blockade (compared with general anaesthesia alone) have also shown a delay in biochemical recurrence of prostate cancer;[12,20] a similar such trial found no difference.[21] Retrospective studies examining the outcomes for colon cancer and major abdominal surgery have either failed to find statistically significant differences between those receiving supplemental epidural analgesia compared with those who are not [13,22,23] or produced mixed results.[14] A study by the authors on the effect of neuraxial anaesthesia in patients having brachytherapy also did not show a significant protective effect. [16]

It is difficult to explain the lack of consistency in treatment effect (if any) for neuraxial supplemental analgesia. Variations in stress response and opioid consumption (with the associated prevention of immune suppression) may affect some cancer and patient populations more than others. Closer examination of many of these studies reveals details of their methodology and inclusion criteria that introduce significant confounding variables. Intention-to-treat analysis is optimal in examining patients' outcome based on their randomisation but inevitably the statistical technique considers patients without effective epidural analgesia to be analysed with groups who have active neuraxial blockade. The success of neuraxial or paravertebral analgesia is rarely considered in trials. Importantly, the most predictive aspects of cancer recurrence - pathological staging and lymphovascular space invasion [24] are often not considered in the analysis of results. Trials that have tightly controlled pathological classification have subsequently shown a benefit for epidural analgesia.[25] The call for randomised, prospective studies is loud. At least one such trial is currently underway.[26]

Cyclo-oxygenase Inhibitors

The rapid escalation in pro-inflammatory cytokines associated with post-operative surgical healing, as well as their known role in immunosuppression make this line of research enquiry appealing for the perioperative management of the oncological patient.

The role of cyclo-oxygenase-2 (COX-2) has come under the most scrutiny. COX-2 has enhanced expression on tumor cells; tumor cells with excessive COX-2 expression are reported to metastasise more frequently.[27] Prostaglandin production by either tumors or the natural stress response after surgical incision would be growth enhancing and deleterious in the face of minimal residual disease after surgery. Seminal research recently published has elegantly demonstrated tumors' capacity to invade and metastasise through the mechanism of Vascular Endothelial Growth Factor – C (VEGFc) stimulated prostaglandin release.[28] Furthermore, in the same study it was shown that the introduction of COX-2 inhibitors reduced the otherwise unimpeded dilation of lymphatic systems.

A small retrospective study did find statistical significance for the use of perioperative ketorolac in the delay of cancer recurrence for patients receiving mastectomy for breast cancer.[29] However, one large prospective study actively sought to examine the potential benefit of COX-2 inhibitors in the prevention of recurrence after colon surgery [30] and found a beneficial trend without statistical significance for reduced rate of recurrence and overall survival.

In the choice of anaesthesia for the cancer patient, there is emerging evidence of the benefit of propofol as a COX-2 inhibitor itself.[31] No randomised or prospective trial yet exists, but animal and in vitro data would suggest that this may become the choice method of delivery of general anaesthesia during cancer resection.

Beta receptor antagonists

The pursuit of a pharmacological blockade for the body's post surgery stress response by the use of beta adrenergic receptor antagonists has extended to studies in cancer. Convincing evidence in animal research exists not only for an enhanced rate of metastasis in mice undergoing tumor resection under conditions of 'stress' compared with baseline, but that the metastasis rate is halved with the use of concurrent beta blockade.[32] Also in the rat model, post-operative administration of beta-blocker and cyclo-oxygenase inhibitors synergistically reduced the metastasis acceleration effects of surgery.[33] Furthermore, a retrospective review of patients treated for hypertension with chronic beta blockade were shown to have reduced rates of cancer recurrence, distant metastasis formation and a longer disease free interval following diagnosis of operable breast cancer.[34] Beta blockade has also been associated with a reduction in VEGF secretion from ovarian tumors and this may provide an insight into the mechanism of beta receptor antagonists' apparent beneficial effect.[35] Beta receptor antagonists have a theoretical role in reducing the surgical stress response and thereby an anti-metastatic function. This has only been demonstrated in animal models but is an exciting area of academic pursuit in human trials.

Perioperative blood transfusion.

The use of a blood transfusion for the perioperative care of a patient receiving surgery for cancer has attracted much attention due to the known Transfusion Related Immunomodulation (TRIM) phenomenon.[36] The consequent effect this may have on the potential for recurrence of cancer has never been answered by randomised controlled trials. A recently updated Cochrane review found that despite wide heterogeneity, data from 36 of the available 237 studies could be used for analysis. A statistically significant association (OR 1.42 [95% Confidence Interval 1.20-1.67]) was found with early recurrence of colorectal cancer.[37] The authors concluded caution with the use of perioperative blood transfusion. The use of leukodepleted blood is perceived to only partially reduce TRIM.[38]

Conclusion:

Retrospective studies examining the role of regional anaesthesia and cyclo-oxygenase inhibitors in the prevention of cancer recurrence have shown inconsistent benefit. The most profound advances in our understanding of perioperative interventions and potential anti-cancer effects have come from animal studies. The

evidence from this research suggests that offsetting the immune suppression and stress response of surgery may be the key mechanism for potential benefit of pharmacological and physiological interventions. While careful attention is required to controlling for the many factors involved in cancer recurrence, this biochemical theory is likely to form the basis for future prospective trials in this field. Nevertheless, today's anaesthetists can already implement the principles of prevention of their patient's stress response to surgery to minimise the chance of cancer returning after surgery.

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