Elsevier Editorial System(tm) for Best Practice & Research: Clinical Anaesthesiology
Manuscript Draft

Manuscript Number: YBEAN-D-13-171

Title: Does regional anaesthesia & analgesia or opioid analgesia influence recurrence after primary cancer surgery? An update of available evidence

Article Type: Issue 27.4

Keywords: anaesthesia; metastases; recurrence; cancer; regional; opioids; NSAIDs

Corresponding Author: Prof Donal J Buggy,

Corresponding Author's Institution: Mater University Hospital

First Author: Simon A Ash, BSc MBBCh DA FCA MMed

Order of Authors: Simon A Ash, BSc MBBCh DA FCA MMed; Donal J Buggy

Abstract: Cancer continues to be a key cause of morbidity and mortality worldwide and its overall incidence continues to increase. Anaesthetists are increasingly faced with the challenge of managing cancer patients, either for surgical resection to debulk or excise the primary tumour, surgical emergencies in patients on chemotherapy, or for the analgesic management of disease- or treatment-related chronic pain. Metastatic recurrence is a concern. Surgery and a number of perioperative factors are suspected to accelerate tumour growth and potentially increase the risk of metastatic recurrence. Retrospective analyses have suggested an association between anaesthetic technique and cancer outcomes, and anaesthetists have sought to ameliorate the consequences of surgical trauma and minimize the impact of anaesthetic interventions. Just how anaesthesia and analgesia impact cancer recurrence and consequent survival is very topical, as understanding the potential mechanisms and interactions impacts on the anaesthetist's ability to contribute to the successful outcome of oncological interventions.

TITLE PAGE

Does regional anaesthesia & analgesia or opioid analgesia influence recurrence after primary cancer surgery? An update of available evidence

Simon A. Ash (First Author)

BSc, MBBCh, DA, FCA, MMed

Research Fellow

Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland

Email: sleepmerchant@icloud.com

Tel: +44 87 183 5715

Donal J. Buggy (Corresponding Author)

MD, MSc, Dip Med Eld, FRCPI, FCAI, FRCA

Professor of Anaesthesia, School of Medicine & Medical Science, University College Dublin

Consultant in Anaesthesia, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland

Email: donal.buggy@ucd.ie

Conflict of interest statement:

None

ABSTRACT

Cancer continues to be a key cause of morbidity and mortality worldwide and its overall incidence continues to increase. Anaesthetists are increasingly faced with the challenge of managing cancer patients, either for surgical resection to debulk or excise the primary tumour, surgical emergencies in patients on chemotherapy, or for the analgesic management of disease- or treatment-related chronic pain. Metastatic recurrence is a concern. Surgery and a number of perioperative factors are suspected to accelerate tumour growth and potentially increase the risk of metastatic recurrence. Retrospective analyses have suggested an association between anaesthetic technique and cancer outcomes, and anaesthetists have sought to ameliorate the consequences of surgical trauma and minimize the impact of anaesthetic interventions. Just how anaesthesia and analgesia impact cancer recurrence and consequent survival is very topical, as understanding the potential mechanisms and interactions impacts on the anaesthetist's ability to contribute to the successful outcome of oncological interventions.

Keywords: anaesthesia; metastases; recurrence; cancer; regional; opioids; NSAIDs

Introduction:

Cancer continues to be a key cause of morbidity and mortality worldwide and its overall incidence continues to increase, despite growing efforts towards its prevention and considerable advances in its treatment.

Worldwide in 2008, it was estimated almost 13 million new cancer cases were diagnosed and over 7 million people died from cancer. In the UK, over a third of people will develop some form of cancer during their lifetime and over 150,000 people died from cancer in 2010 (http://www.cancerresearchuk.org/cancer-info/cancerstats/keyfacts [Accessed 20 July 2013]) . In the USA in 2013, it is estimated that over 1.6 million new cases will be diagnosed, and every day over 1,500 people will die from cancer.[1]

Anaesthetists are increasingly faced with the challenge of managing cancer patients, either for surgical resection to debulk or excise the primary tumour, the mainstay of treatment in many forms of cancer (particularly solid tumours), or for the analgesic management of disease- or treatment-related chronic pain in a proportion of the increasing number of people living with or overcoming cancer, concurrent with improvements in oncological therapies.[2-4]

Metastatic recurrence is a concern and occurs commonly. While the pattern of tumour growth is usually non-linear, with periods of dormancy alternating with periods of growth [5-8], surgery potentially alters this pattern. Examination of the hazard rate of recurrence subsequent to primary tumour resection has shown that while progression of initially dormant micro-metastases does not seem to be subject to direct induction by surgery, early recurrence during

the first two postoperative years may be.[9-13]

As surgery is suspected to accelerate tumour growth and potentially increase the risk of metastatic recurrence, anaesthetists have sought to ameliorate the consequences of surgical trauma and minimize the impact of anaesthetic interventions.[14] A number of perioperative factors have been suggested to directly affect tumour cells and impact on cell-mediated immunity potentially enhancing the risk of metastatic recurrence.[15-17] There is, therefore, a strong rationale for the development of perioperative techniques to lower the risk of cancer recurrence.

How anaesthesia and analgesia impact cancer recurrence and consequent survival is very topical,[4, 18-21] as understanding the potential mechanisms and interactions impacts on the anaesthetist's ability to contribute to the successful outcome of oncological interventions.

How does metastasis occur and how might it be influenced:

The metastatic process is intricate. Beginning with the detachment of metastatic cells from the primary tumour, metastasis depends on the essential processes of first angiogenesis, to establish an independent blood supply, and evasion of the host's immune mechanisms. This culminates in proliferation of metastasis within a distant organ(s).[15]

Cancer cells result from a single cell rendered 'genetically unstable' by multiple cycles of division, mutated and susceptible to the acquisition of further mutations.[22] Mutation renders this cell resistant to the normal regulation of cell division, enabling uncontrolled cellular proliferation.[23] However, an evolving tumour cannot progress beyond a 2mm

diameter without angiogenesis occurring to meet its increasing metabolic requirements.[24] The tumour releases pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and prostaglandin E_2 (PGE_2), to initiate and maintain vascular and lymphatic angiogenesis leading to the formation of a new capillary network.[25]

A collection of cancer cells may then separate from the primary tumour mass and penetrate the neighboring tissues. Tumour cells enter the systemic circulation by breaching the basement membranes of thin-walled vessels, including lymphatics, heralding the conversion from benign carcinoma in-situ to invasive malignant tumour. Once within the systemic circulation, these cells then migrate to the capillary bed of a distant organ, where proliferation continues resulting in the formation of a tumour secondary (metastasis).

The conclusion of the metastatic process depends on the specific cancer's metastatic predisposition (type, stage and site) and on a multitude of interactions between the tumour cells and the host's immune system.

Interaction between the immune system and cancer cells:

The developing tumour induces an inflammatory state resulting in the recruitment of immune cells. Cell-mediated immunity forms the principle defense against cancer cell invasion, with less than one in a thousand invading cancer cells viable after 24 hours. However, even with intact immunity, some cancer cells will elude the host's defences and continue to grow.

The major components of cell-mediated immunity include natural killer (NK) cells, cytotoxic T-cells (CTC), mononuclear cells, macrophages, and dendritic cells. NK cells, CTC and dendritic cells are involved in controlling tumour development.[26-28] NK cells are large, granular cytotoxic lymphocytes that provoke the early lysis of tumour cells spontaneously, without requiring prior sensitization to these tumour cells.[16, 29] A decrease in NK cell activity has been associated with the promotion of breast cancer growth and metastasis in an experimental rat model.[30] Similarly decreased NK cell numbers have been associated with an increased susceptibility to cancer, or metastases post oncological surgery.[31] Increased NK cell activity correlates with resistance to metastasis.[32-34] CTC form part of adaptive immunity, becoming sensitized to tumour cells (via the presentation of tumour-specific antigens by dendritic cells) and lysing them. Tumour infiltration by CTC has been associated with a positive prognosis in colorectal cancer.[35]

However, recruited immune cells may not all favour tumour eradication. The CD11b+ subset of macrophages recognize metastatic breast cancer cells and these tumour-associated macrophages (TAM) aid their progression.[36] Tumour-associated neutrophils (TAN) produce reactive oxygen species, growth factors and PGE_2, aiding tumour growth and tumour spread.[37, 38] Myeloid-derived suppressor cells inhibit NK cell and CTC activities.[39]

Likewise, the immune system is modulated by multiple cytokines, which may paradoxically hinder or assist cancer progression.[40] Pro-inflammatory cytokines may favour tumour progression.[41] Inflammation may play a central role in cancer, with increased levels of interleukin (IL)-1, tumour necrosis factor alpha (TNF-α) and PGE_2 associated with negative effects on tumour progression.[26] PGE_2 inhibits the function of

dendritic cells and thereby CTC. [42, 43] It also inhibits the cytotoxic activity of NK cells and CTC.[9] Inflammation also influences the differentiation and dissemination of cancer cells, accelerating their growth rate, and potentially also inhibits anticancer immunity disrupting the balance between proliferation and eradication.[26, 44, 45]

Manipulation of the immune system may form the basis of neoadjuvant oncological therapies, aimed at increasing the anticancer response. For example, perioperative immune stimulation has shown a potential survival benefit in a rat model[46] and recombinant NK cells could have therapeutic potential.[47]

In the same manner, the mechanisms by which surgery, anaesthesia and analgesia may affect the immune response and cancer cellular pathways are complex and multi-factorial.[48] These mechanisms may include direct and/or indirect effects on cellular immunity (whether impeding or facilitating tumour growth), tumour cells themselves (affecting metabolism and mitotic capacity), extracellular matrix and the balance of angiogenic factors (influencing metastatic capability).

Several studies have demonstrated the effects of anaesthesia and analgesia on host defences and their possible effect on tumour growth and spread.[32, 49, 50] This immune modulation combined with the surgical stress and inflammatory response and possible direct effects of drugs on the cancer cells themselves may create perioperative conditions advantageous to cancer cells.[51-53] Additionally adjuvant oncological treatment tends not to be commenced in the immediate postoperative period to facilitate patient's recovery, allowing for the establishment and spread of perioperative micro-metastases.[16, 54, 55]

This has led to a focus on perioperative factors that may be modified in order to tip the balance in favour of reduced cancer spread and recurrence.[31]

How surgery may influence recurrence:

While the surgical excision of a primary tumour forms an essential part of multimodal oncological treatment, offering a particular prognostic advantage in the treatment of solid tumours, the surgical process can inadvertently aid the metastatic process.[56] Animal models have demonstrated surgical enhancement of tumour growth and metastasis, including a significant increase in number of metastases and tumour retention.[32-34, 57, 58] Colorectal cancer metastases to the liver have also been shown to have accelerated growth rate after surgery.[59]

The presence of circulating cancer cells after excision of histologically negative margins, whether pre-existing micro-metastases escaping dormancy or the additional unintentional dissemination of tumour emboli during surgery, is independently associated with increased risk of cancer recurrence and decreased disease-free survival in colorectal[60-62] and breast cancer.[63-65]

The consequence of these residual cancer cells depends on the tumour's genotype,[5] phenotype and environment, as influenced by the host's immune competence,[26] as outlined above. However, the inflammatory reaction triggered by surgery potentially plays a major role in the early risk of recurrence during the first two postoperative years.[10-13] Major surgery, which cancer surgery typically is, is characterised by both a neuroendocrine (hypothalamic-pituitary axis and sympathetic nervous system) and a cytokine mediated stress response [66]

commensurate to the degree of surgical trauma, transiently suppressing cell-mediated immunity, particularly NK cell activity, in the host (in direct proportion to the magnitude of the stress response) during the critical period when fate of residual cancer cells may be determined.[67]

Additionally, surgery may, again inadvertently, facilitate the metastatically essential process of lymphovascular angiogenesis. The process of angiogenesis is regulated by pro-angiogenic factors [including VEGF, fibroblast growth factor and transforming growth factor beta (TGF β)] and anti-angiogenic factors [including endostatin (an endogenous mediator formed by the fragmentation of collagen) and angiostatin], which exist in a fragile balance. Growth factors and inflammatory mediators, including PGE_2, are involved after tissue injury during postoperative wound healing and may mediate metastatic progression.[62, 68, 69]

Anti-angiogenic factors have been shown to decrease metastasis of lung cancer cells in a mouse model.[70] However, surgery potentially lowers these anti-angiogenic factors and has been shown to increase pro-angiogenic factors in patients undergoing mastectomy for breast cancer [71] and animal models of ovarian cancer.[72, 73] Furthermore, surgical stress has an effect on matrix-metalloproteinases (MMPs), the proteolytic enzymes that facilitate the penetration of the extracellular matrix and basement membrane during the metastatic process.[53]

Concurrent factors also need consideration, some of which may neither be directly related to surgery nor amenable to the anaesthetist's intervention. Older age, female gender and tumour node metastasis status are associated with decreased cancer-free survival.[74] A history of depression may predict tumour recurrence and overall survival,[75] presumably secondary to

the effects of perioperative psychological stress and anxiety on the neuroendocrine stress response exerting a significant effect on the micro-environment of the tumour or micro-metastases. Barron and colleagues, in a small retrospective study that should be interpreted cautiously, [76] found that the non-selective β-adrenoreceptor antagonist, propranolol, is associated with a diminution in the proportion of detrimental stress effects thereby lowering the incidence of cancer-related mortality.

Other concurrent perioperative factors can potentially be ameliorated by the anaesthetist's actions, including hypoxia, hyperglycaemia, hypotension, allogeneic blood transfusion and inadvertent intraoperative hypothermia.[4] As allogeneic blood transfusion modulates the host immune system, it may also influence cancer recurrence.[77] As transfused leucocytes potentially alter circulating lymphocyte ratios and function, irradiated or leucocyte-depleted red-cells are frequently preferentially administered to oncology patients. However, even where leucocyte-depleted red cells are used, transfusion has been associated with decreased cancer-free survival and decreased overall survival in lung cancer [78] and a recent meta-analysis by Churchhouse and colleagues [79], while not reaching definitive conclusions, suggested an association between transfusion and decreased cancer-free survival. Interestingly, a recent animal study found that erythrocytes rather than leucocytes are implicated in the cancer-promoting effects of both autologous and allogeneic blood transfusions.[80]

Intraoperative hypothermia is common, whether as a result of blunted thermoregulation or the theatre environment, and alters host immunity at a cellular level with inhibition of antigen presentation and decreased cytokine secretion. Moslemi-Kebria and colleagues, in a

retrospective study,[81] demonstrated a significant decrease in overall survival for a cohort of patients experiencing hypothermia (< 36^{o}C) during debulking of advanced ovarian cancer.

How anaesthesia and analgesia may influence recurrence:

Before discussing the potential mechanisms how anaesthesia and analgesia may affect cancer recurrence, with or without modulation of the immune system, it is important to note that effective postoperative analgesia may facilitate resistance to metastasis [82] and that a high level of perioperative immune-suppression has been observed in animal models where acute postoperative pain was highest.[34, 83-86]

Several studies [11, 74, 87-93] have suggested that perioperative anaesthetic and analgesic techniques and drugs may affect postoperative inflammation and immune function.

Volatile agents

Volatile agents have been associated with immune-modulation and potentially increased tumour metastasis in-vitro and in experimental animal models. The possible mechanisms are multiple: decreasing NK cell activity,[94] interfering with lymphocyte antigen activity [95] and inducing apoptosis in T-lymphocytes [96] and B-lymphocytes.[97]

Furthermore, volatile agents may have direct effects on cancer cells. Volatile agents have been shown to alter cancer cell gene expression in-vitro.[98] Tavare and colleagues [99] have suggested that volatile agents upregulate hypoxia-inducible factor (HIF- 1α) in cancer cells. HIF-1α increases angiogenesis and has a resultant association with poor prognosis. However,

volatile agents may also have positive effects: migration of colon cancer cells was decreased, following the inhibition of MMPs release from neutrophils pre-treated with sevoflurane and desflurane.[100]

Non-volatile agents

The non-volatile anaesthetic gas, nitrous oxide (N_2O), and the anaesthetic induction agents have also received scrutiny of their immune modulating effects and potential effects on cancer recurrence. Used concurrently with isoflurane and remifentanil, N_2O demonstrated no difference in cancer recurrence in patients undergoing colectomy for cancer.[101] Ketamine and thiopentone, in an inoculation animal model of breast cancer, have been shown to suppress NK cell activity with a related increase in breast cancer tumour metastasis.[94] Ketamine has demonstrated effects on cellular immunity in laboratory models, including inhibition of T lymphocyte maturation [102] and NK cell cytotoxicity,[32] both albeit at supraclinical concentrations. Clinically, low dose ketamine (0.15mg/kg) has been shown to suppress NK cell cytotoxicity and inhibit the production of pro-inflammatory cytokines (IL-6 and TNF-α).[103]

On the other hand, propofol may have an anti-neoplastic effect, decreasing the production of PGE_2 by monocytes in vitro.[104] It did not suppress NK cell cytotoxicity in a rat model of breast cancer, nor was it associated with an increase in tumour recurrence.[94]

Local anaesthetics

Local anaesthetics (LAs) are suggested to have anti-proliferative and cytotoxic effects on cancer cells in a number of in-vitro studies. Lidocaine has been shown to inhibit epidermal growth factor in-vitro, decreasing the proliferation of tongue cancer cells.[105] It has also been shown to alter the DNA methylation status of certain breast cancer cell lines and is associated with the re-activation of tumour suppressor genes.[106] Lidocaine and bupivacaine (racemic and isomer specific) inhibited transcription pathways associated with the initiation and metastasis of cancer and decreased mesenchymal stem cell proliferation in-vitro.[107] Werdehausen and colleagues [108] demonstrated the cytotoxicity of eight local anaesthetic agents on T-lymphoma cells in-vitro, with the magnitude of their cytotoxicity correlating with individual potency and lipophilicity.

Adjuncts

Lastly, the anaesthetic adjunct clonidine, an α2-adrenoceptor agonist, has been shown to alter NK cell activity and augment cellular proliferation in-vitro and in experimental animals.[32] The stimulation of α2-adrenoceptors, present on certain breast cancer cells, increases proliferation of these cells.[109]

Of particular interest is the anaesthetist's approach towards analgesia, perhaps beginning with opioid use as the effects of morphine on cancer appeared in the literature as early as 1962.[110]

How opioids may influence cancer recurrence:

Opioids are routinely used as postoperative analgesics, forming a key part of the armamentarium for the management of cancer pain, whether disease or treatment-related chronic pain or acute postoperative pain.

Clinical evidence surrounding the effect of opioids on cancer processes is limited. However, in addition to their analgesic effects, opiates are known to exert immunomodulatory effects which may impact on cancer progression and recurrence. A range of mechanisms and cancer effects have been suggested, both beneficial and detrimental. Immunosuppression has been documented in-vitro and in-vivo, in both animal models and humans. Opioids suppress immune function via inhibition of both humoral and cell-mediated immunity,[18, 111] however, not all to the same degree or in the same way (with morphine being the most studied). Fentanyl has been shown to decrease NK cell function in a rat model for up to 8 days.[32] Franchi and colleagues [112] demonstrated a mu opioid receptor (MOR)-mediated reduction of toll-like receptor expression by morphine in a mouse model. Both the promotion and inhibition of tumour cell growth has been shown.[50, 113-117]

The evidence overall is conflicting, with discrepant results prevalent.[9, 48, 74, 88-93] Interpretation of the evidence is complicated by the fact that much of the literature is retrospective and comprehensive data on actual opioid use is variable, with the potential confounding influences of opiate type, dose, route of administration, duration of exposure unknown.[9, 18] The effect of tolerance or withdrawal and tumour cell specificity have also been proposed to account for the conflicting evidence.[118] Similarly, it may not be possible to create a tumour environment completely devoid of the influences of opioids, as human physiology includes an endogenous opioid system.

The pro- or anti-cancer effects of this endogenous opioid system remain poorly understood. The endogenous pathways point predominantly to anti-cancer effects and exogenous opioids to pro-cancer effects. The reason is unclear, given that both endogenous and exogenous opioids act on the MOR. β-Endorphin has effects on immunity and the surgical stress response, and has been touted as possible anti-cancer therapeutic agent.[119] Potential anti-neoplastic effects of increased β-endorphin include the augmentation of NK cell cytotoxicity and attenuation of the stress response (by favouring anti-inflammatory cytokines).

The potential effects of the endogenous opioid system are not limited to the endogenous hormones. Indeed, changes at a receptor level may also have an impact on the effects of both endogenous and exogenous opioids. The MOR has been studied in this regard.

Stressing the interaction between the opioid and immune systems, inflammatory cytokines (IL-1, IL-4, IL-6 and TNF) have been shown to regulate MOR gene expression.[120] In-vitro and in-vivo rodent models of subtypes of lung cancer have demonstrated upregulation of MOR, resulting in amplified tumour growth and metastases. Silencing MOR expression or using methylnaltrexone, a peripheral MOR antagonist, appeared to negate the opioid-induced effects on tumour growth and metastasis.[121-123] A synergistic effect between methynaltrexone and other chemotherapeutic agents has been demonstrated, potentially decreasing unwanted side-effects of cytotoxic agents by reducing the therapeutic dose required.[124]

Polymorphisms of the MOR gene are also relevant. A single-nucleotide polymorphism of the MOR gene (A118G), already shown to decrease the analgesic response to opioids,[125, 126] has been associated with a significantly increased probability of survival at 10 years in a recent study of 2,039 women with breast cancer by Bortsov and colleagues.[127] However, cautious interpretation is recommended because of a number of limiting factors, including omission of data on patient perception of pain, adequacy of pain control, the use of strong opioids and ongoing oncological treatments.[18]

Opioids, particularly morphinergic pathways through their stimulation of MOR, have been suspected to directly increase tumour growth rate.[123] Morphine has been shown to stimulate tumour cell migration and proliferation in human endothelial cells in-vitro.[128] Proposed mechanisms for effects of tumour growth rate include enhanced angiogenesis, including enhancing cyclooxygenase-2 (COX-2) and increased PGE_2 production,[129] and activation of VEGF and epidermal growth factor.[130] When studied in a breast cancer cell line, while demonstrating no direct proliferative effect, morphine has also been linked to augmented production of urokinase plasminogen activator (UPA).[131] With a similar morphine-induced increase in secretion of UPA in human colon cancer cells,[132] an association between morphine and the metastatic potential of these tumours may exist as UPA promotes tumour invasion and metastasis. There is some evidence that aprotinin, a serine protease inhibitor with UPA-inhibitory effects, may improve cancer survival if used in the perioperative setting.[133]

Moreover, the activation of specific genes (“genetic switching”) during the perioperative period is theorised to contribute to cancer recurrence. Breast cancer cells, which express MOR, demonstrated a morphine-induced increase in cell migration, possibly mediated by the

activation of the NET1 gene.[51] The NET1 gene has been shown to promote cancer cell migration in adenocarcinoma. “Genetic switching” at tumour microvascular level triggered by opioids is also mediated by TAMs, likely via adrenergic signalling.

Avoiding opioids may positively impact cancer recurrence when alternative pain management strategies are possible. However, while single-dose or low-dose opioids can potentially promote tumour growth, extended exposure to high concentrations may suppress tumour growth.[117] Chronic high-dose morphine has been shown to attenuate angiogensis in an in vitro murine model of lung cancer, with decreased tumour progression and an associated significant reduction in VEGF secretion under hypoxic conditions.[118]

Opioids may also decrease tumour adhesion, migration and proliferation. Morphine has been shown to decrease MMPs and increase MMP inhibitors in a dose-dependent manner. Potentially mediated by the nitric oxide (NO) system, morphine has inhibited MMP production in breast cancer cell lines (MMP-2 and MMP-9) [115] and colon cancer cancer cells.[134]

Moreover, the NO pathway is associated with morphine’s induction of apoptosis in human endothelial cells, with activation of nuclear factor (NF)-κB.[135] NF-κB is a potent transcription factor in the regulation of inflammation and apoptosis. At clinically relevant doses, morphine also induces in-vitro apoptosis in lung cancer and promyelocytic leukaemia cell lines.[136]

Given that there may be a rationale for avoiding or minimizing opioid use, there has been investigation into whether the opioid-sparing effects of non-steroidal anti-inflammatory

drugs (NSAIDs) and regional anaesthesia and analgesia may have beneficial anti-cancer effects.

How NSAIDs may influence cancer recurrence:

Owing to their effects on COX-2 and PGE_2, major mediators in cancer progression,[38] NSAIDs have a strong potential anti-cancer effect.[27] The inhibition of PGE_2 production, secondary to COX-2 inhibition, may have direct impact on cancer cell mutation, proliferation and survival. Its suppression may also have beneficial effects on cell-mediated immunity, increasing the cytotoxicity of NK cells and CTC.[9] Key enzymes that control the production of prostaglandins, cyclooxygenases (COX-1 and COX-2), prototypic targets of the NSAIDs, are frequently over-expressed or deregulated in the progression of cancer.

COX-2 expression has been linked to multiple aspects of the metastatic process, including bone marrow metastasis.[137-141] In murine models of breast cancer, COX-2 has been shown to be involved in osteoclastogenesis (via IL-11)[138] and stimulation of osteoclasts to resorb bone (via PGE2 and IL-8).[139] It has also been associated with increased tumourgenicity and clonogenicity, conferring genomic instability and changes in cell cycle regulation, including resistance to anoikis, as well as resistance to chemotherapeutic agents (including doxorubicin).[142-146] COX-2 has also been associated with cancer cell migration.[146] Recent data also suggest an intersection of lymphangiogenic growth factor signaling and the prostaglandin pathways in the control of metastatic spread via the lymphatic vasculature.[38]

The association between COX-2 expression and cancer recurrence and survival has been studied recently in a number of cancer types.[147-152] COX-2 expression has been associated with increased cancer recurrence[147] and forms a prognostic marker of poor outcome.[150, 152] Its expression has been associated with decreased survival[149] and its inhibition with decreased mortality[148, 151]. A recent meta-analysis of observational studies in patients with ovarian cancer by Lee and colleagues[148] suggested that increased COX-2 expression may be an independent risk factor for decreased overall survival.

The use of NSAIDs, most commonly aspirin, to inhibit COX-2 and the subsequent effects on cancer outcomes have also been studied. Aspirin has been associated with reduced all-cause and colorectal cancer-specific mortality,[153] reduced prostate cancer-specific mortality.[154] It has also been associated with better outcomes following prostate radiation therapy[155] and lower recurrence in patients with colorectal cancer.[156]

Rothwell and colleagues[157] recently conducted a pooled analysis of 51 randomised, controlled trials studying the effects of daily aspirin use in the prevention of vascular events and found a significant decrease in overall cancer mortality in both men and women after three to five years of aspirin use. Similarly, Jacobs and colleagues[158] demonstrated a reduction in cancer mortality associated with daily aspirin use, regardless of duration, in their retrospective analysis of a pooled US cohort (over 100,000 individuals).

The role of NSAIDs in anti-cancer therapy, including its role as a perioperative strategy (likely mediated through a reduction in inflammation), remains unclear, with the choice

of drug, optimum dose, optimum timing and ideal duration unknown. Their utilisation seems primarily limited by the unwanted side-effects associated with chronic use.[151, 159-164] More research is needed into various non-specific and COX-2 specific NSAIDs, safer enteric and non-enteric delivery mechanisms and timing and duration of treatment.

Given concerns over the side-effects of chronic NSAID use, there is particular interest as to whether or not regional anaesthesia offers an advantage over traditional general anaesthesia techniques and whether the avoidance of opioid analgesia through regional analgesia techniques, often to decrease non-cancer related opioid side effects, offers an advantage with regards to cancer outcome and recurrence.

How regional anaesthesia and analgesia may influence cancer recurrence:

Proposed theoretical benefits of regional anaesthesia may be indirect, including a decreased surgical stress response with subsequent amelioration of the associated effects on host immunity, reduced opioid and intraoperative volatile anaesthetic requirements, optimised analgesia and the aforementioned potential anti-cancer effects of the local anaesthetic agents themselves.[107, 165, 166] The combination of some or all of these proposed effects could theoretically alter the perioperative balance of pro-tumour and anti-tumour influences.

Regional anaesthesia may influence the expression of several cytokines expressed perioperatively, including IL-4 and IL-10 [167], which may directly or indirectly influence the immune system response to residual cancer cells post-surgery.

There are a number of studies suggesting regional anaesthesia exerts a positive effect on anti-cancer immunity and cancer metastasis.[33, 34, 58, 83-86] Bar-Yosef and colleagues [84] found that the addition of spinal anaesthesia to general anaesthesia, compared with general anaesthesia alone, decreased lung metastasis post laparotomy in a rat model. Similarly, spinal anaesthesia has been associated with preservation of NK cell function in a mouse model.[58]

However, conflicting evidence regarding the anti-cancer effect of regional anaesthesia exists. With regards to the mechanism whereby regional anaesthesia may mediate an anti-cancer effect, Conrick-Martin and colleagues [29] conducted a recent meta-analysis which found, when compared with general anaesthesia, there was no association between regional anaesthesia and the retention of NK cell function. Similarly, the presence of a regional anaesthetic technique (a continuous paravetrebral block) was not associated with an alteration in the concentrations of pro-angiogenic factors (VEGF and PGE_2), associated with cancer metastasis and subsequent recurrence, in patients undergoing surgery for breast cancer.[25]

As even a small improvement in cancer recurrence attributable to anaesthesia technique would potentially bring large benefits for patients and cost-savings for healthcare systems,[168] the literature contains a number of retrospective analyses of the potential association between regional anaesthesia and cancer recurrence.[87-92, 169-181] A renewed interest was brought about by a retrospective study by Exadaktylos and colleagues [87] which found an association between reduced recurrence in breast cancer patients undergoing mastectomy and axillary node clearance receiving paravertebral anaesthesia and analgesia compared with patients who received GA and opioid analgesia, subsequent retrospective analyses across a variety of cancer surgery types has yielded conflicting results.

While an association with decreased cancer recurrence or recurrence risk has been demonstrated in several cancers (breast cancer,[87] prostate cancer,[88] ovarian cancer,[172] laryngeal cancer,[178] melanoma[175] and a subset of colon cancer patients [91]), no difference in cancer recurrence has been shown in others (localised prostate cancer,[92] cervical cancer,[169] colon cancer [74, 91, 176]) and ovarian cancer [177]).

Likewise, while investigators have demonstrated improved survival or a trend towards improved survival,[90, 92, 170, 171, 175, 176, 178, 181, 182] others have found no change in survival rates,[74, 89, 169, 170, 174, 177, 179] or found the demonstrated improved survival absent in the presence of pre-existing metastases.[90]

Results within a study may also be counter-intuitive or conflicting. Cummings and colleagues [176] conducted a large database study of a retrospective population of over 42,000 patients and found that while there was no difference in cancer recurrence associated with the addition of epidural analgesia compared with general anaesthesia alone, there was a significant improvement in five-year survival. Wuethrich and colleagues [92] found an improvement in clinical progression-free survival, but not in recurrence-free, cancer-specific or overall survival in prostate cancer patients. A further retrospective analysis by members of the same group concluded that regional anaesthesia (epidural) was not associated with a decreased risk of cancer progression nor increased survival after radical prostatectomy in prostate cancer patients at high risk of progression.[179]

Possible variations in the perioperative milieu that potentially alter cancer outcomes (whether surgical or anaesthetic) and the fact that patient groups are in-homogenous, with different grades of histology, stage, and presence or absence of lymphovascular space infiltration

(LVSI), create difficulty in the interpretation of retrospective studies and the follow-up analyses of multicentre trials. It remains unclear what factors associated with regional anaesthesia techniques are most likely to impact outcomes, including duration and effectiveness of epidural, degree of opioid-sparing effect and degree of sympatholysis. In addition, the perioperative care that a patient receives is multidisciplinary. Multifactoral elements of pre- and postoperative care aimed at surgical recovery, including nutrition and fluid management, may influence outcomes.[183]

Several potential confounding factors affect the interpretation of the existing evidence. These may be potential methodological problems, including with outcome measures and end-point choices, whether in the assessment of recurrence (e.g. biochemical [88, 92] vs. referral for oncological treatment [176]) or the absence of a standardized definition of survival (clinical progression free [92] vs. recurrence-free vs. overall).[184] Likewise, survival or recurrence data does not differentiate between the early recurrence thought to be due to perioperative factors and later recurrence due to reactivation of dormant micro-metastases not influenced by the perioperative period.[9] Analytical anomalies may also occur, such as overfitting in multivariate analyses [9, 93, 184] and selection bias, to which retrospective studies are inherently susceptible.

Failure to report, analyse or control for potentially clinically significant impact factors as mentioned above (duration and effectiveness of regional anaesthesia, whether initiated pre-intra- or postoperatively, cancer stage and LVSI state) is also problematic. Unintentional hypothermia, allogenic blood transfusion and aforementioned anaesthesia- and surgery-independent influencers of cancer-free survival aside, opioids, NSAIDs, β-blockers and α-agonists, which may themselves impact cancer outcomes, may have been given during the

perioperative period, whether as part of multimodal analgesia protocols, rescue analgesia for inadequate regional anaesthesia or, indeed, as a part of the regional anaesthetic technique. Likewise, the type and amount of intra-operative volatile anaesthetic, or absence thereof with total intravenous anaesthesia (TIVA), used for maintenance of general anaesthesia may have an impact. Finally, as the patient's perioperative inflammatory status may be a major prognostic determinant[185], the absence of its assessment is noteworthy.

While the effects of regional anaesthesia may ultimately be tumour or tumour cell specific, as suggested by increased inhibitory effects of propofol-paravertebral anaesthesia/analgesia on oestrogen-receptor negative breast cancer,[52] the current literature is useful only in the formulation of hypotheses by underscoring the associations that exist.

A causal link, if it exists, will only be confirmed by prospective, randomised control trials, which are urgently needed. Controlling for confounding factors, whether by matching groups for surgery-independent and anaesthesia-independent factors or analysing the effects of individual drugs, will hopefully broaden our understanding of this topic.

Conclusion:

There is some in-vitro and in-vivo experimental and retrospective clinical evidence linking anaesthetic/analgesic techniques with cancer outcomes and recurrence. Opioids, LAs and NSAIDs exert effects on cancer biology and NSAIDs and regional techniques may be beneficial through their avoidance of opioids. However, it is unclear as to whether avoidance of opioid analgesia may always benefit cancer patients, whether

NSAIDs can be safely used or how regional anaesthesia and analgesia should be used to have a potential benefit.

The avoidance of opioids and, indeed, the suggestion that they may be detrimental in the absence of conclusive evidence, may have a negative impact on patient care. The denial of adequate analgesia and consequent potential increase in surgical stress response and chronic pain is especially noteworthy, as, while the exact cause/effect relationship remains unclear, cancer patients without chronic pain have a lower mortality than those who do.[186]

Because only prospective, randomised, control trials can provide or prove a causal link, more research is urgently required. We eagerly await the results of current ongoing clinical trials, although we may only see them in a half a decade.

Currently, none of the evidence conclusively supports changing routine anaesthetic practice for oncology patients undergoing surgery, nor does the evidence preclude anaesthesiologists from using multimodal analgesic techniques to improve pain control, reduce opioid requirements, reduce the surgical stress response and decrease inflammation.

Practice Points:

- Cancer-associated pain, whether acute or chronic, requires treatment.
- While there is ongoing research on the potential effect of anaesthesia and analgesia on recurrence or metastasis, there is currently no evidence to justify altering anaesthetic technique in cancer patients.

- Cancer patients should continue to receive best practice anaesthetic technique in accordance with their own decisions and co-morbidities, as discussed with their individual anaesthetist.
- The focus should be on good analgesia, amelioration of the stress response and reduction of inflammation as best practice.

Research Agenda:

- Completion of ongoing prospective randomized trials on the effect of anaesthetic technique on cancer outcome.
- Evaluating an animal model of the effect of local anaesthetic lidocaine on cancer recurrence and, if promising, progressing to a clinical randomized trial of the effect of IV lidocaine on cancer outcome.
- Translational and experimental investigation of the effect of anaesthetics and analgesics on cancer cell biology and the human immune response to it.

References:

1. American Cancer Society: Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013.
2. Colvin L, Forbes K, Fallon M. Difficult pain. BMJ 2006; **332(7549)**:1081-1083.
3. Harrington CB, Hansen JA, Moskowitz M et al. It's not over when it's over: long-term symptoms in cancer survivors--a systematic review. Int J Psychiatry Med 2010; **40(2)**:163-181.
4. Kurosawa S: Anesthesia in patients with cancer disorders. Curr Opin Anaesthesiol 2012; **25(3)**:376-384.
5. Schmidt-Kittler O, Ragg T, Daskalakis A et al: From latent disseminated cells to overt metastasis: genetic analysis of systemic breast cancer progression. Proc Nat Acad Sci USA 2003; **100(13)**:7737-7742.
6. Almog N, Ma L, Raychowdhury R et al. Transcriptional switch of dormant tumors to fast-growing angiogenic phenotype. Cancer Res 2009; **69(3)**:836-844.
7. Aguirre-Ghiso JA. The problem of cancer dormancy: understanding the basic mechanisms and identifying therapeutic opportunities. Cell Cycle 2006; **5(16)**:1740-1743.
8. Demicheli R, Terenziani M, Valagussa P et al. Local recurrences following mastectomy: support for the concept of tumor dormancy. J Nat Cancer Inst 1994; **86(1)**:45-48.
9. Forget P, Coulie PG, Retsky M et al. Is there a rationale for an anesthesiologist's role against cancer recurrence? Acta Anaesthesiol Belg 2013; **64(1)**:15-24.
10. Retsky M. New concepts in breast cancer emerge from analyzing clinical data using numerical algorithms. Int J Environ Res Public Health 2009; **6(1)**:329-348.

11. Forget P, Vandenhende J, Berliere M et al. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. Anesth Analg 2010; **110(6)**:1630-1635.

12. Demicheli R, Biganzoli E, Boracchi P et al. Recurrence dynamics does not depend on the recurrence site. Breast Cancer Res 2008; **10(5)**:R83.

13. Arimidex TAoiCTG, Forbes JF, Cuzick J et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008; **9(1)**:45-53.

14. Varani J, Lovett EJ, 3rd, Lundy J. A model of tumor cell dormancy: effects of anesthesia and surgery. J Surg Oncol 1981; **17(1)**:9-14.

15. Talmadge JE, Fidler IJ. AACR centennial series: the biology of cancer metastasis: historical perspective. Cancer Res 2010; **70(14)**:5649-5669.

16. Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth 2010; **105(2)**:106-115.

17. Kavanagh T, Buggy DJ. Can anaesthetic technique effect postoperative outcome? Curr Opin Anaesthesiol 2012; **25(2)**:185-198.

18. Colvin LA, Fallon MT, Buggy DJ. Cancer biology, analgesics, and anaesthetics: is there a link? Br J Anaesth 2012; **109(2)**:140-143.

19. Heaney A, Buggy DJ. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis? Br J Anaesth 2012; **109 Suppl 1**:i17-i28.

20. Niwa H, Rowbotham DJ, Lambert DG, Buggy DJ. Can anesthetic techniques or drugs affect cancer recurrence in patients undergoing cancer surgery? J Anesth 2013. (in print)

21. Mao L, Lin S, Lin J. The effects of anesthetics on tumor progression. Int J Physiol Pathophysiol Pharmacol 2013; **5(1)**:1-10.

22. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 2003; **3(6)**:453-458.

23. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; **144(5)**:646-674.

24. Langley RR, Fidler IJ. The seed and soil hypothesis revisited--the role of tumor-stroma interactions in metastasis to different organs. Int J Cancer 2011; **128(11)**:2527-2535.

25. O'Riain SC, Buggy DJ, Kerin MJ et al. Inhibition of the stress response to breast cancer surgery by regional anesthesia and analgesia does not affect vascular endothelial growth factor and prostaglandin E2. Anesth Analg 2005; **100(1)**:244-249.

26. Demaria S, Pikarsky E, Karin M et al. Cancer and inflammation: promise for biologic therapy. J Immunother 2010, **33(4)**:335-351.

27. Hussain M, Javeed A, Ashraf M et al. Non-steroidal anti-inflammatory drugs, tumour immunity and immunotherapy. Pharmacol Res 2012; **66(1)**:7-18.

28. Kurosawa S, Matsuzaki G, Harada M et al. Early appearance and activation of natural killer cells in tumor-infiltrating lymphoid cells during tumor development. Eur J Immunol 1993; **23(5)**:1029-1033.

29. Conrick-Martin I, Kell MR, Buggy DJ: Meta-analysis of the effect of central neuraxial regional anesthesia compared with general anesthesia on postoperative natural killer T lymphocyte function. J Clin Anesth 2012; **24(1)**:3-7.

30. Ben-Eliyahu S, Page GG, Yirmiya R, Shakhar G. Evidence that stress and surgical interventions promote tumor development by suppressing natural killer cell activity. Int J Cancer 1999; **80(6)**:880-888.

31. Gottschalk A, Sharma S, Ford J et al. Review article: the role of the perioperative period in recurrence after cancer surgery. Anesth Analg 2010; **110(6)**:1636-1643.

32. Forget P, Collet V, Lavand'homme P, De Kock M. Does analgesia and condition influence immunity after surgery? Effects of fentanyl, ketamine and clonidine on natural killer activity at different ages. Eur J Anaesthesiol 2010; **27(3)**:233-240.

33. Forget P, De Kock M. [Could anaesthesia, analgesia and sympathetic modulation affect neoplasic recurrence after surgery? A systematic review centred over the modulation of natural killer cells activity]. Ann Fr Anesth Reanim 2009; **28(9)**:751-768.

34. Shakhar G, Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: could they reduce recurrence rates in oncological patients? Ann Surg Oncol 2003; **10(8)**:972-992.

35. Pages F, Berger A, Camus M et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. N Engl J Med 2005; **353(25)**:2654-2666.

36. Qian B, Deng Y, Im JH et al. A distinct macrophage population mediates metastatic breast cancer cell extravasation, establishment and growth. PLoS One 2009; **4(8)**:e6562.

37. Di Carlo E, Forni G, Musiani P. Neutrophils in the antitumoral immune response. Chem Immunol Allergy 2003; **83**:182-203.

38. Karnezis T, Shayan R, Caesar C et al. VEGF-D promotes tumour metastasis by regulating prostaglandins produced by the collecting lymphatic endothelium. Cancer Cell 2012; **21(2)**:181-195

39. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. J Immunol 2009; **182(8)**:4499-4506.

40. Dinarello CA. The paradox of pro-inflammatory cytokines in cancer. Cancer Metastasis Rev 2006; **25(3)**:307-313.

41. Raman D, Baugher PJ, Thu YM, Richmond A. Role of chemokines in tumor growth. Cancer Lett 2007; **256(2)**:137-165.

42. Waymack JP, Flescher E, Venkatraman J et al. Effect of prostaglandin E in multiple experimental models. VIII. Effect on host response to metastatic tumor. J Surg Oncol 1991; **48(4)**:239-245.

43. Okuno K, Jinnai H, Lee YS et al. A high level of prostaglandin E2 (PGE2) in the portal vein suppresses liver-associated immunity and promotes liver metastases. Surg Today 1995; **25(11)**:954-958.

44. Demicheli R, Retsky MW, Hrushesky WJ, Baum M. Tumor dormancy and surgery-driven interruption of dormancy in breast cancer: learning from failures. Nat Clin Pract Oncol 2007; **4(12)**:699-710.

45. Demicheli R, Retsky MW, Hrushesky WJ et al. The effects of surgery on tumor growth: a century of investigations. Ann Oncol 2008; **19(11)**:1821-1828.

46. Goldfarb Y, Sorski L, Benish M et al. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. Ann Surg 2011; **253(4)**:798-810.

47. Motohashi S, Nakayama T. Natural killer T cell-mediated immunotherapy for malignant diseases. Front Biosci 2009; **1**:108-116.

48. Afsharimani B, Cabot P, Parat MO. Morphine and tumor growth and metastasis. Cancer Metastasis Rev 2011; **30(2)**:225-238.

49. Kawaraguchi Y, Horikawa YT, Murphy AN et al. Volatile anesthetics protect cancer cells against tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis via caveolins. Anesthesiol 2011; **115(3)**:499-508.

50. Panagiotou S, Bakogeorgou E, Papakonstanti E et al. Opioid agonists modify breast cancer cell proliferation by blocking cells to the G2/M phase of the cycle: involvement of cytoskeletal elements. J Cell Biochem 1999; **73(2)**:204-211.

51. Ecimovic P, Murray D, Doran P et al. Direct effect of morphine on breast cancer cell function in vitro: role of the NET1 gene. Br J Anaesth 2011; **107(6)**:916-923.

52. Deegan CA, Murray D, Doran P et al. Effect of anaesthetic technique on oestrogen receptor-negative breast cancer cell function in vitro. Br J Anaesth 2009; **103(5)**:685-690.

53. Deegan CA, Murray D, Doran P et al. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. Reg Anesth and Pain Med 2010; **35(6)**:490-495.

54. Baum M, Demicheli R, Hrushesky W, Retsky M. Does surgery unfavourably perturb the "natural history" of early breast cancer by accelerating the appearance of distant metastases? Eur J Cancer 2005; **41(4)**:508-515.

55. Singleton PA, Moss J. Effect of perioperative opioids on cancer recurrence: a hypothesis. Future Oncol 2010; **6(8)**:1237-1242.

56. Neeman E, Ben-Eliyahu S. Surgery and stress promote cancer metastasis: new outlooks on perioperative mediating mechanisms and immune involvement. Brain Behav Immun 2013; **30 Suppl**:S32-40.

57. Benish M, Bartal I, Goldfarb Y et al. Perioperative use of beta-blockers and COX-2 inhibitors may improve immune competence and reduce the risk of tumor metastasis. Ann Surg Oncol 2008; **15(7)**:2042-2052.

58. Wada H, Seki S, Takahashi T et al. Combined spinal and general anesthesia attenuates liver metastasis by preserving TH1/TH2 cytokine balance. Anesthesiol 2007; **106(3)**:499-506.

59. Peeters CF, de Waal RM, Wobbes T et al. Outgrowth of human liver metastases after resection of the primary colorectal tumor: a shift in the balance between apoptosis and proliferation. Int J Cancer 2006; **119(6)**:1249-1253.

60. Peach G, Kim C, Zacharakis E et al. Prognostic significance of circulating tumour cells following surgical resection of colorectal cancers: a systematic review. Br J Cancer 2010; **102(9)**:1327-1334.

61. Lloyd JM, McIver CM, Stephenson SA et al. Identification of early-stage colorectal cancer patients at risk of relapse post-resection by immunobead reverse transcription-PCR analysis of peritoneal lavage fluid for malignant cells. Clin Cancer Res 2006; **12(2)**:417-423.

62. Iinuma H, Watanabe T, Mimori K et al. Clinical significance of circulating tumor cells, including cancer stem-like cells, in peripheral blood for recurrence and prognosis in patients with Dukes' stage B and C colorectal cancer. J Clin Oncol 2011; **29(12)**:1547-1555.

63. Molloy TJ, Bosma AJ, Baumbusch LO et al. The prognostic significance of tumour cell detection in the peripheral blood versus the bone marrow in 733 early-stage breast cancer patients. Breast Cancer Res 2011; 13(3):R61.

64. Bidard FC, Vincent-Salomon A, Gomme S et al. Disseminated tumor cells of breast cancer patients: a strong prognostic factor for distant and local relapse. Clin Cancer Res 2008; **14(11)**:3306-3311.

65. Park Y, Kitahara T, Urita T et al. Expected clinical applications of circulating tumor cells in breast cancer. World J Clin Oncol 2011; **2(8)**:303-310.

66. Buggy DJ, Smith G. Epidural anaesthesia and analgesia: better outcome after major surgery?. Growing evidence suggests so. BMJ 1999; **319(7209)**:530-531.

67. Goldfarb Y, Ben-Eliyahu S. Surgery as a risk factor for breast cancer recurrence and metastasis: mediating mechanisms and clinical prophylactic approaches. Breast Dis 2006; **26**:99-114.

68. Bogden AE, Moreau JP, Eden PA. Proliferative response of human and animal tumours to surgical wounding of normal tissues: onset, duration and inhibition. Br J Cancer 1997; **75(7)**:1021-1027.

69. Hofer SO, Shrayer D, Reichner JS et al. Wound-induced tumor progression: a probable role in recurrence after tumor resection. Arch Surg 1998; **133(4)**:383-389.

70. Wang HL, Ning T, Li M et al. Effect of endostatin on preventing postoperative progression of distant metastasis in a murine lung cancer model. Tumori 2011; **97(6)**:787-793.

71. Looney M, Doran P, Buggy DJ. Effect of anesthetic technique on serum vascular endothelial growth factor C and transforming growth factor beta in women undergoing anesthesia and surgery for breast cancer. Anesthesiol 2010; **113(5)**:1118-1125.

72. Lee JW, Shahzad MM, Lin YG et al. Surgical stress promotes tumor growth in ovarian carcinoma. Clin Cancer Res 2009; **15(8)**:2695-2702.

73. Thaker PH, Han LY, Kamat AA et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med 2006; **12(8)**:939-944.

74. Myles PS, Peyton P, Silbert B et al. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. BMJ 2011; **342**:d1491.

75. Bjorneklett HG, Lindemalm C, Rosenblad A et al. A randomised controlled trial of support group intervention after breast cancer treatment: results on anxiety and depression. Acta Oncol 2012; **51(2)**:198-207.

76. Barron TI, Connolly RM, Sharp L et al. Beta blockers and breast cancer mortality: a population- based study. J Clin Oncol 2011; **29(19)**:2635-2644.

77. Weber RS, Jabbour N, Martin RC 2nd. Anemia and transfusions in patients undergoing surgery for cancer. Ann Surg Oncol 2008; **15(1)**:34-45.

78. Ng T, Ryder BA, Chern H et al. Leukocyte-depleted blood transfusion is associated with decreased survival in resected early-stage lung cancer. J Thorac Cardiovasc Surg 2012; **143(4)**:815-819.

79. Churchhouse AM, Mathews TJ, McBride OM, Dunning J. Does blood transfusion increase the chance of recurrence in patients undergoing surgery for lung cancer? Interact Cardiovasc Thorac Surg 2012; **14(1)**:85-90.

80. Atzil S, Arad M, Glasner A et al. Blood transfusion promotes cancer progression: a critical role for aged erythrocytes. Anesthesiol 2008; **109(6)**:989-997.

81. Moslemi-Kebria M, El-Nashar SA, Aletti GD, Cliby WA. Intraoperative hypothermia during cytoreductive surgery for ovarian cancer and perioperative morbidity. Obstet Gynecol 2012; **119(3)**:590-596.

82. Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain 2001; **90(1-2)**:191-199.

83. Page GG, McDonald JS, Ben-Eliyahu S. Pre-operative versus postoperative administration of morphine: impact on the neuroendocrine, behavioural, and metastatic-enhancing effects of surgery. Br J Anaesth 1998; **81(2)**:216-223.

84. Bar-Yosef S, Melamed R, Page GG et al. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. Anesthesiol 2001; **94(6)**:1066-1073.

85. Beilin B, Shavit Y, Hart J et al. Effects of anesthesia based on large versus small doses of fentanyl on natural killer cell cytotoxicity in the perioperative period. Anesth Analg 1996; **82(3)**:492-497.

86. Liljefors M, Nilsson B, Hjelm Skog AL et al. Natural killer (NK) cell function is a strong prognostic factor in colorectal carcinoma patients treated with the monoclonal antibody 17-1A. Int J Cancer 2003; **105(5)**:717-723.

87. Exadaktylos AK, Buggy DJ, Moriarty DC et al. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiol 2006; **105(4)**:660-664.

88. Biki B, Mascha E, Moriarty DC et al. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiol 2008, **109(2)**:180-187.

89. Tsui BC, Rashiq S, Schopflocher D et al. Epidural anesthesia and cancer recurrence rates after radical prostatectomy. Can J Anaesth 2010; **57(2)**:107-112.

90. Christopherson R, James KE, Tableman M et al. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. Anesth Analg 2008; **107(1)**:325-332.

91. Gottschalk A, Ford JG, Regelin CC et al. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. Anesthesiol 2010; **113(1)**:27-34.

92. Wuethrich PY, Hsu Schmitz SF, Kessler TM et al. Potential influence of the anesthetic technique used during open radical prostatectomy on prostate cancer-related outcome: a retrospective study. Anesthesiol 2010; **113(3)**:570-576.

93. Forget P, Tombal B, Scholtes JL et al. Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? Eur J Anaesthesiol 2011; **28(12)**:830-835.

94. Melamed R, Bar-Yosef S, Shakhar G et al. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by

propofol: mediating mechanisms and prophylactic measures. Anesth Analg 2003; **97(5)**:1331-1339.

95. Yuki K, Astrof NS, Bracken C et al. Sevoflurane binds and allosterically blocks integrin lymphocyte function-associated antigen-1. Anesthesiol 2010; **113(3)**:600-609.

96. Loop T, Dovi-Akue D, Frick M et al. Volatile anesthetics induce caspase-dependent, mitochondria-mediated apoptosis in human T lymphocytes in vitro. Anesthesiol 2005; **102(6)**:1147-1157.

97. Wei H, Liang G, Yang H et al. The common inhalational anesthetic isoflurane induces apoptosis via activation of inositol 1,4,5-trisphosphate receptors. Anesthesiol 2008; **108(2)**:251-260.

98. Huitink JM, Heimerikxs M, Nieuwland M et al. Volatile anesthetics modulate gene expression in breast and brain tumor cells. Anesth Analg 2010; **111(6)**:1411-1415.

99. Tavare AN, Perry NJ, Benzonana LL et al. Cancer recurrence after surgery: direct and indirect effects of anesthetic agents. Int J Cancer 2012; **130(6)**:1237-1250.

100. Muller-Edenborn B, Roth-Z'graggen B, Bartnicka K et al. Volatile anesthetics reduce invasion of colorectal cancer cells through down-regulation of matrix metalloproteinase-9. Anesthesiol 2012; **117(2)**:293-301.

101. Fleischmann E, Marschalek C, Schlemitz K et al. Nitrous oxide may not increase the risk of cancer recurrence after colorectal surgery: a follow-up of a randomized controlled trial. BMC Anesthesiol 2009; **9**:1.

102. Ohta N, Ohashi Y, Fujino Y. Ketamine inhibits maturation of bone marrow-derived dendritic cells and priming of the Th1-type immune response. Anesth Analg 2009; **109(3)**:793-800.

103. Beilin B, Rusabrov Y, Shapira Y et al. Low-dose ketamine affects immune responses in humans during the early postoperative period. Br J Anaesth 2007; **99(4)**:522-527.

104. Inada T, Kubo K, Shingu K. Possible link between cyclooxygenase-inhibiting and antitumor properties of propofol. J Anesth 2011; **25(4)**:569-575.

105. Sakaguchi M, Kuroda Y, Hirose M. The antiproliferative effect of lidocaine on human tongue cancer cells with inhibition of the activity of epidermal growth factor receptor. Anesth Analg 2006; **102(4)**:1103-1107.

106. Lirk P, Berger R, Hollmann MW, Fiegl H. Lidocaine time- and dose-dependently demethylates deoxyribonucleic acid in breast cancer cell lines in vitro. Br J Anaesth 2012; **109(2)**:200-207.

107. Lucchinetti E, Awad AE, Rahman M et al. Antiproliferative effects of local anesthetics on mesenchymal stem cells: potential implications for tumor spreading and wound healing. Anesthesiol 2012; **116(4)**:841-856.

108. Werdehausen R, Braun S, Fazeli S et al. Lipophilicity but not stereospecificity is a major determinant of local anaesthetic-induced cytotoxicity in human T-lymphoma cells. Eur J Anaesthesiol 2012; **29(1)**:35-41.

109. Luthy IA, Bruzzone A, Pinero CP et al. Adrenoceptors: non conventional target for breast cancer? Curr Med Chem 2009; **16(15)**:1850-1862.

110. Sobel H, Bonorris G. Effect of morphine on rats bearing Walker carcinosarcoma 256. Nature 1962; **196**:896-897.

111. Afsharimani B, Cabot PJ, Parat MO. Morphine use in cancer surgery. Front Pharmacol 2011; **2**:46.

112. Franchi S, Moretti S, Castelli M et al. Mu opioid receptor activation modulates Toll like receptor 4 in murine macrophages. Brain Behav Immun 2012; **26(3)**:480-488.

113. Tegeder I, Grosch S, Schmidtko A et al. G protein-independent G1 cell cycle block and apoptosis with morphine in adenocarcinoma cells: involvement of p53 phosphorylation. Cancer Res 2003; **63(8)**:1846-1852.

114. Lazarczyk M, Matyja E, Lipkowski AW. A comparative study of morphine stimulation and biphalin inhibition of human glioblastoma T98G cell proliferation in vitro. Peptides 2010; **31(8)**:1606-1612.

115. Gach K, Szemraj J, Wyrebska A, Janecka A. The influence of opioids on matrix metalloproteinase-2 and -9 secretion and mRNA levels in MCF-7 breast cancer cell line. Mol Biol Rep 2011; **38(2)**:1231-1236.

116. Gach K, Wyrebska A, Fichna J, Janecka A. The role of morphine in regulation of cancer cell growth. Naunyn-Schmiedebergs Arch Pharmacol 2011; **384(3)**:221-230.

117. Lin X, Wang YJ, Li Q et al. Chronic high-dose morphine treatment promotes SH-SY5Y cell apoptosis via c-Jun N-terminal kinase-mediated activation of mitochondria-dependent pathway. FEBS J 2009; **276(7)**:2022-2036.

118. Koodie L, Ramakrishnan S, Roy S. Morphine suppresses tumor angiogenesis through a HIF-1alpha/p38MAPK pathway. Am J Pathol 2010; **177(2)**:984-997.

119. Sarkar DK, Murugan S, Zhang C, Boyadjieva N. Regulation of cancer progression by beta-endorphin neuron. Cancer Res 2012; **72(4)**:836-840.

120. Kraus J. Regulation of mu-opioid receptors by cytokines. Front Biosci 2009; **1**:164-170.

121. Lennon FE, Mirzapoiazova T, Mambetsariev B et al. Overexpression of the mu-opioid receptor in human non-small cell lung cancer promotes Akt and mTOR activation, tumor growth, and metastasis. Anesthesiol 2012; **116(4)**:857-867.

122. Lennon FE, Moss J, Singleton PA. The mu-opioid receptor in cancer progression: is there a direct effect? Anesthesiol 2012; **116(4)**:940-945.

123. Mathew B, Lennon FE, Siegler J et al. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. Anesth Analg 2011; **112(3)**:558-567.

124. Singleton PA, Garcia JG, Moss J. Synergistic effects of methylnaltrexone with 5-fluorouracil and bevacizumab on inhibition of vascular endothelial growth factor-induced angiogenesis. Mol Cancer Ther 2008; **7(6)**:1669-1679.

125. Hayashida M, Nagashima M, Satoh Y et al. Analgesic requirements after major abdominal surgery are associated with OPRM1 gene polymorphism genotype and haplotype. Pharmacogenomics 2008; **9(11)**:1605-1616.

126. Kasai S, Hayashida M, Sora I, Ikeda K. Candidate gene polymorphisms predicting individual sensitivity to opioids. Naunyn-Schmiedebergs Arch Pharmacol 2008; **377(4-6)**:269-281.

127. Bortsov AV, Millikan RC, Belfer I et al. mu-Opioid receptor gene A118G polymorphism predicts survival in patients with breast cancer. Anesthesiol 2012, **116(4)**:896-902.

128. Singleton PA, Lingen MW, Fekete MJ et al. Methylnaltrexone inhibits opiate and VEGF-induced angiogenesis: role of receptor transactivation. Microvasc Res 2006, 72(1-2):3-11.

129. Farooqui M, Li Y, Rogers T et al. COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. Br J Cancer 2007; **97(11)**:1523-1531.

130. Fujioka N, Nguyen J, Chen C et al. Morphine-induced epidermal growth factor pathway activation in non-small cell lung cancer. Anesth Analg 2011; **113(6)**:1353-1364.

131. Gach K, Szemraj J, Fichna J et al. The influence of opioids on urokinase plasminogen activator on protein and mRNA level in MCF-7 breast cancer cell line. Chem Biol Drug Des 2009; **74(4)**:390-396.

132. Nylund G, Pettersson A, Bengtsson C et al. Functional expression of mu-opioid receptors in the human colon cancer cell line, HT-29, and their localization in human colon. Dig Dis Sci 2008; **53(2)**:461-466.

133. Norman PH, Thall PF, Purugganan RV et al. A possible association between aprotinin and improved survival after surgery for mesothelioma. Cancer 2009; 115(4):833-841.

134. Harimaya Y, Koizumi K, Andoh T et al. Potential ability of morphine to inhibit the adhesion, invasion and metastasis of metastatic colon 26-L5 carcinoma cells. Cancer Lett 2002; **187(1-2)**:121-127.

135. Hsiao PN, Chang MC, Cheng WF et al. Morphine induces apoptosis of human endothelial cells through nitric oxide and reactive oxygen species pathways. Toxicology 2009; **256(1-2)**:83-91.

136. Hatsukari I, Hitosugi N, Ohno R et al. Induction of apoptosis by morphine in human tumor cell lines in vitro. Anticancer Res 2007; **27(2)**:857-864.

137. Singh B, Berry JA, Shoher A et al. COX-2 involvement in breast cancer metastasis to bone. Oncogene 2007; **26(26)**:3789-3796.

138. Singh B, Berry JA, Shoher A, Lucci A. COX-2 induces IL-11 production in human breast cancer cells. J Surg Res 2006; **131(2)**:267-275.

139. Singh B, Berry JA, Vincent LE, Lucci A. Involvement of IL-8 in COX-2-mediated bone metastases from breast cancer. J Surg Res 2006; **134(1)**:44-51.

140. Lucci A, Krishnamurthy S, Singh B et al. Cyclooxygenase-2 expression in primary breast cancers predicts dissemination of cancer cells to the bone marrow. Breast Cancer Res Treat 2009; **117(1)**:61-68.

141. Singh B, Cook KR, Vincent L et al. Role of COX-2 in tumorospheres derived from a breast cancer cell line. J Surg Res 2011; **168(1)**:e39-49.

142. Singh B, Vincent L, Berry JA et al. Cyclooxygenase-2 expression induces genomic instability in MCF10A breast epithelial cells. J Surg Res 2007; **140(2)**:220-226.

143. Singh B, Cook KR, Vincent L et al. Cyclooxygenase-2 induces genomic instability, BCL2 expression, doxorubicin resistance, and altered cancer-initiating cell phenotype in MCF7 breast cancer cells. J Surg Res 2008; **147(2)**:240-246.

144. Singh B, Irving LR, Tai K, Lucci A. Overexpression of COX-2 in celecoxib-resistant breast cancer cell lines. J Surg Res 2010; **163(2)**:235-243.

145. Tsujii M. Cyclooxygenase, cancer stem cells and DNA methylation play important roles in colorectal carcinogenesis. Digestion 2013; **87(1)**:12-16.

146. Guo YC, Chang CM, Hsu WL et al. Indomethacin inhibits cancer cell migration via attenuation of cellular calcium mobilization. Molecules 2013; **18(6)**:6584-6596.

147. Brand L, Munding J, Pox CP et al.: ss-catenin, Cox-2 and p53 immunostaining in colorectal adenomas to predict recurrence after endoscopic polypectomy. Int J Colorectal Dis 2013; **28(8)**:1091-1098.

148. Lee JY, Myung SK, Song YS. Prognostic role of cyclooxygenase-2 in epithelial ovarian cancer: a meta-analysis of observational studies. Gynecol Oncol 2013; **129(3)**:613-619.

149. Chen YF, Luo RZ, Li Y et al. High expression levels of COX-2 and P300 are associated with unfavorable survival in laryngeal squamous cell carcinoma. Eur Arch Otorhinolaryngol 2013; **270(3)**:1009-1017.

150. Ke HL, Tu HP, Lin HH et al. Cyclooxygenase-2 (COX-2) up-regulation is a prognostic marker for poor clinical outcome of upper tract urothelial cancer. Anticancer Res 2012; **32(9)**:4111-4116.

151. Kraus S, Naumov I, Arber N. COX-2 active agents in the chemoprevention of colorectal cancer. Recent Results Cancer Res 2013; **191**:95-103.

152. Al-Maghrabi J, Buhmeida A, Emam E et al. Cyclooxygenase-2 expression as a predictor of outcome in colorectal carcinoma. World J Gastroenterol 2012; **18(15)**:1793-1799.

153. McCowan C, Munro AJ, Donnan PT, Steele RJ. Use of aspirin post-diagnosis in a cohort of patients with colorectal cancer and its association with all-cause and colorectal cancer specific mortality. Eur J Cancer 2013; **49(5)**:1049-1057.

154. Choe KS, Cowan JE, Chan JM et al. Aspirin use and the risk of prostate cancer mortality in men treated with prostatectomy or radiotherapy. J Clin Oncol 2012; **30(28)**:3540-3544.

155. Zaorsky NG, Buyyounouski MK, Li T, Horwitz EM. Aspirin and statin nonuse associated with early biochemical failure after prostate radiation therapy. Int J Radiat Oncol Biol Phys 2012; **84(1)**:e13-17.

156. Benamouzig R, Uzzan B, Deyra J et al.: Prevention by daily soluble aspirin of colorectal adenoma recurrence: 4-year results of the APACC randomised trial. Gut 2012; **61(2)**:255-261.

157. Rothwell PM, Price JF, Fowkes FG et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012; **379(9826)**:1602-1612.

158. Jacobs EJ, Newton CC, Gapstur SM, Thun MJ. Daily aspirin use and cancer mortality in a large US cohort. J Natl Cancer Inst 2012; **104(16)**:1208-1217.

159. Singh B, Lucci A. Role of cyclooxygenase-2 in breast cancer. J Surg Res 2002; **108(1)**:173-179.

160. Holmes MD, Chen WY, Li L et al. Aspirin intake and survival after breast cancer. J Clin Oncol 2010; **28(9)**:1467-1472.

161. Burn J, Gerdes AM, Macrae F et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011; **378(9809)**:2081-2087.

162. Wang D, Dubois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene 2010; **29(6)**:781-788.

163. Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. Nat Rev Clin Oncol 2012; 9(5):259-267.

164. Ferrandez A, Piazuelo E, Castells A. Aspirin and the prevention of colorectal cancer. Best Prac Res Clin Gastroenterol 2012; **26(2)**:185-195.

165. Lopes AG, Jr., Rodrigues CJ, Lopes LH et al. Differences in tumour growth, tumour cell proliferation and immune function after laparoscopy and laparotomy in an animal model. HPB 2001; **3(3)**:213-217.

166. Sessler DI. Does regional analgesia reduce the risk of cancer recurrence? A hypothesis. Eur J Cancer Prev 2008; **17(3)**:269-272.

167. Moselli NM, Baricocchi E, Ribero D et al. Intraoperative epidural analgesia prevents the early proinflammatory response to surgical trauma. Results from a prospective randomized clinical trial of intraoperative epidural versus general analgesia. Ann Surg Oncol 2011; **18(10)**:2722-2731.

168. Yeager MP, Rosenkranz KM. Cancer recurrence after surgery: a role for regional anesthesia? Reg Anesth Pain Med 2010; **35(6)**:483-484.

169. Ismail H, Ho KM, Narayan K, Kondalsamy-Chennakesavan S. Effect of neuraxial anaesthesia on tumour progression in cervical cancer patients treated with brachytherapy: a retrospective cohort study. Br J Anaesth 2010; **105(2)**:145-149.

170. Gupta A, Bjornsson A, Fredriksson M et al. Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery:

a retrospective analysis of data from 655 patients in central Sweden. Br J Anaesth 2011; **107(2)**:164-170.

171. Lin L, Liu C, Tan H et al. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. Br J Anaesth 2011; **106(6)**:814-822.

172. de Oliveira GS, Jr., Ahmad S, Schink JC et al. Intraoperative neuraxial anesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. Reg Anesth Pain Med 2011; **36(3)**:271-277.

173. Lai R, Peng Z, Chen D et al. The effects of anesthetic technique on cancer recurrence in percutaneous radiofrequency ablation of small hepatocellular carcinoma. Anesth Analg 2012; **114(2)**:290-296.

174. Day A, Smith R, Jourdan I et al. Retrospective analysis of the effect of postoperative analgesia on survival in patients after laparoscopic resection of colorectal cancer. Br J Anaesth 2012; **109(2)**:185-190.

175. Gottschalk A, Brodner G, Van Aken HK et al. Can regional anaesthesia for lymph-node dissection improve the prognosis in malignant melanoma? Br J Anaesth 2012, **109(2)**:253-259.

176. Cummings KC 3rd, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. Anesthesiol 2012; **116(4)**:797-806.

177. Lacassie HJ, Cartagena J, Branes J et al. The relationship between neuraxial anesthesia and advanced ovarian cancer-related outcomes in the chilean population. Anesth Analg 2013; **117(3)**:653-660.

178. Merquiol F, Montelimard AS, Nourissat A et al. Cervical epidural anesthesia is associated with increased cancer-free survival in laryngeal and hypopharyngeal cancer

surgery: a retrospective propensity-matched analysis. Reg Anesth Pain Med 2013; **38(5)**:398-402.

179. Wuethrich PY, Thalmann GN, Studer UE, Burkhard FC. Epidural Analgesia during Open Radical Prostatectomy Does Not Improve Long-Term Cancer-Related Outcome: A Retrospective Study in Patients with Advanced Prostate Cancer. PLoS One 2013; **8(8)**:e72873.

180. Binczak M, Tournay E, Billard V et al. Major abdominal surgery for cancer: does epidural analgesia have a long-term effect on recurrence-free and overall survival? Ann Fr Anesth Reanim 2013; **32(5)**:e81-88.

181. Chen WK, Miao CH. The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. PLoS One 2013; **8(2)**:e56540.

182. Smith TJ, Staats PS, Deer T et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. J Clin Oncol 2002; **20(19)**:4040-4049.

183. Varadhan KK, Neal KR, Dejong CH et al. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr 2010; **29(4)**:434-440.

184. Forget P, Leonard D, Kartheuser A, De Kock M. Endpoint selection and unreported analgesic use may render oncologic studies inconclusive. Anesthesiol 2011; **114(3)**:717; author reply 718.

185. Proctor MJ, Morrison DS, Talwar D et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. Eur J Cancer 2011; **47(17)**:2633-2641.

186. Macfarlane GJ, McBeth J, Silman AJ. Widespread body pain and mortality: prospective population based study. BMJ 2001; **323(7314)**:662-665.