Onco-Anaesthesia – Improving Long Term Cancer Outcomes

Professor Bernhard Riedel

Peter MacCallum Cancer Centre and the University of Melbourne, Australia

Cancer is a leading cause of death worldwide. Surgery is the primary and most effective treatment for most solid tumours.[1, 2] As such, two-thirds of cancer patients (~10 million patients annually and 45 million by 2030) require cancer surgery; >80% of cancer patients require anaesthesia for curative or supportive therapy.[1, 2] Minimum residual disease from tumour cell dissemination is unavoidable given that cancer cells are often circulating in the blood stream at diagnosis. This may predispose patients to scattered micro-metastases. Consequently, despite surgical treatment, cancer recurrence occurs in many patients—usually as metastases in organs distant from the primary tumour. Metastases impose a significant health burden and are responsible for more than 90% of cancer deaths.[3] Several perioperative (surgical and anaesthetic) factors may accelerate progression of such minimal residual disease.

Strikingly, a number of recent retrospective clinical cohort studies provide evidence that choice of anaesthesia during cancer resection surgery is linked to cancer recurrence. In a substantial review[4] we highlighted that the perioperative period during cancer surgery is accompanied by stress, inflammation, supressed cell-mediated immunity and increased pro-angiogenic and growth factors (e.g. VEGF) aimed at promoting wound healing. Together, these factors also promote local and distant growth of malignant tissue. Additionally, anaesthetic agents are implicated in inflammatory processes and in immunomodulation. Specifically, inhalational anaesthesia (with volatile agents such as sevoflurane) impairs the primary host defence (especially Natural Killer [NK] cells, which resist residual cancer cells after tumour resection),[5] promotes pro-inflammatory effects on macrophages (with compelling evidence that macrophages contribute to metastasis formation[3]), and up-regulates anti-apoptotic, hypoxia inducible factor-1 alpha (HIF-1α), VEGF[6] and PI3K-Akt pathway signalling.[7] In contrast, propofol-TIVA and lidocaine anaesthesia enhance host defenses (NK cells) and have anti-inflammatory effects on macrophages,[8-10] and down regulates mTOR, p53, p38 MAPK and MMP signalling.[7] Amide local anaesthetics (e.g. lidocaine, the internationally preferred name for lignocaine), commonly used as an intravenous infusion for analgesia during general anaesthesia,[11] also exhibit immune preserving and anti-inflammatory properties.[9, 10]

Intravenous general anaesthetic agent (propofol) may reduce cancer recurrence

Alarmingly, a systematic review and meta-analysis[12] of retrospective observational clinical studies[13-15] suggests that traditional inhalational anaesthesia is associated with a decrease in both disease-free survival (DFS) and overall survival (OS) when compared with the alternative of total intravenous anaesthesia using propofol (propofol-TIVA). Our animal experiments support this: when cancer resections are performed with propofol-TIVA or with intravenous lidocaine infusion (*vs*. volatile anaesthesia alone) cancer progression is decreased.

A large, retrospective cohort study by Wigmore *et al.*[15] evaluated >7,000 patients treated at The Royal Marsden Cancer Hospital (London, UK); roughly half were given volatile anaesthesia, with the others given propofol-TIVA for cancer surgery. The hazard ratio for death over median 2.6 years (with propensity matched anaesthetic approach) was 0.68 for propofol-TIVA *vs*. volatile (95% CI: 0.60-0.78); P<0.001) and 16% *v*s. 23% for mortality observed 5 years after surgery, favouring propofol-TIVA anaesthesia. Wigmore observed the strongest signal within the subgroup of patients with gastrointestinal tract cancers (HR=1.68 volatile *vs*. TIVA, 95% CI: 1.33-2.12; P<0.001). Similar survival benefits are reported in a retrospective analysis of 2,840 Swedish patients with colorectal and breast cancer,[13] in a smaller study of Korean patients with breast cancer,[14] and more recently in a study of 897 propensity matched Chinese patients having gastrectomy for cancer surgery.[16]

Translational research by Buggy and colleagues has found a positive association with propofol-TIVA with regional anaesthesia on *ex-vivo* immune cell function in breast cancer patients (compared with patients who had received volatile anaesthesia) with preservation of NK immune cell function against breast cancer cells[17] and more breast cancer cell apoptosis.[18] A systematic review of the studies to date indicates that propofol-TIVA might in fact be the preferred anaesthetic choice in cancer surgery.[12] Similarly, our meta-analysis of these retrospective studies found that propofol-TIVA, when compared with volatile, associates with improved overall survival (HR=0.73, 95% CI: 0.62-0.86; P<0.01) and improved DFS (HR=0.70, 95% CI: 0.56-0.89; p<0.01). However, the overall evidence for these anaesthetic techniques is currently low quality and a randomised clinical trial is urgently needed.[4]

Lidocaine as an intravenous analgesic may reduce cancer recurrence

Intravenous infusions of lidocaine are increasingly used as an analgesic adjunctive therapy with general anaesthesia for opioid-sparing and anti-inflammatory effects e.g. reduced pain and ileus.[11, 19, 20] Currently ERAS guidelines have a strong recommendation for perioperative use of intravenous lidocaine to enhance postoperative recovery after elective colorectal surgery. When administered intravenously, lidocaine has a wide therapeutic margin and appears to be safe for extended durations up to 24 hours postoperatively.[11]

Given the large overlap between inflammatory signalling pathways and cancer,[4, 21, 22] it is not surprising that amide local anaesthetic drugs may affect cancer pathways. While the cancer biology of lidocaine is complex, lidocaine has been shown to inhibit invasiveness of non-small cell lung cancer cells through inhibition of Src protein tyrosine kinase (Src-dependent mechanisms),[9] and in colon cancer cells through inhibition of Src-independent mechanisms, by blocking voltage-gated sodium channels.[23] Lidocaine also inhibits activation of metalloproteinase-9 (MMP-9), an enzyme

necessary for the degeneration of the extracellular matrix by malignant cells.[24] *In vitro*, lidocaine, at clinically relevant concentrations, preserved cytotoxicity of isolated human NK cells[10] and in clinical studies preserved lymphocyte response and T-helper (Th) Th1/Th2 balance after surgery.[25] This provides the intriguing potential to 'repurpose' lidocaine, a commonly used drug that is safe, affordable, and available worldwide,[26] for preserving perioperative immune function during cancer surgery and substantiates the need for urgent randomised controlled trials to test lidocaine's adjunctive effects in the cancer setting.

Propofol, lidocaine, and volatile anaesthesia are all commonly used in clinical practice, with equipoise in the evidence base and among practicing clinicians. Our survey of 1,000 Australian and New Zealand anaesthetists found that 50% of anaesthetists believe that anaesthetic technique does not affect cancer outcomes and >80% use volatile anaesthesia in preference to propofol-TIVA. Compelling prospective clinical evidence is urgently needed to guide clinical practice.

NSAIDS & B-Blockers:

An increasing number of reviews outline the rationale and early evidence for the adaptation of anaesthetic techniques and the strategic use of anti-adrenergic, anti-inflammatory, and/or antithrombotic therapies. These findings raise the possibility that perioperative modulation of neural signalling or inflammation might offset surgery-related immunosuppression and reduce the malignant potential of residual cancer cells. Many of these strategies are currently under evaluation in large-cohort trials and hold promise as affordable, readily available interventions that will improve the postoperative recurrence-free survival of patients with cancer.

In preclinical studies, propranolol has been shown to inhibit a variety of β-adrenoceptor-mediated processes including tumour cell invasion, angiogenesis, lymphangiogenesis, and epithelial-to-mesenchymal transition. A recent randomized double-blind clinical trial translated these preclinical findings into the clinical trial setting. Women were prescribed either the combination of propranolol (40 mg daily) plus the NSAID etodolac (800 mg daily) or placebo for 5 days before breast cancer surgery and for 5 days after surgery.[27] The investigators found that drug treatment, compared with placebo, partially mitigated the postoperative increase in inflammation as indicated by serum IL-6 levels (4.4-fold versus 5.7-fold increase, respectively; $P < 0.001$) and serum C-reactive protein levels (6.3-fold versus 8.3-fold increase, respectively; $P < 0.001$), both of which are markers of the severity of the surgical stress response. Propranolol plus etodolac, compared with placebo, also prevented the preoperative increase in inflammatory marker levels (IL-6, 11% versus 24%, $P < 0.0009$; C-reactive protein, 10% versus 41%, $P < 0.034$), suggesting that preoperative anxiety primes patients' stress responses before surgery. Notably, drug treatment also reduced the expression of several tumour-promoting genes including transcription factors involved in the promotion of metastasis, recruitment of myeloid cell types, and epithelial-to-mesenchymal transition. These findings demonstrate that brief inhibition of perioperative neural or pro-inflammatory signalling reduces the malignant potential of tumour cells at the time of surgery. Defining the relative contributions of β-blockers and NSAIDs to these effects will be important. Zhou et al.[28] examined the effect of propranolol (60 mg daily) on postoperative peripheral immune cell numbers. Treatment with propranolol was commenced on the day of mastectomy and was found to mitigate against postoperative elevation of circulating Treg cell numbers and suppression of a tumour-antigen-specific CD4+ T cell response. These findings raise the possibility that perioperative modulation of neural signalling or inflammation might offset surgery-related immunosuppression and reduce the malignant potential of residual cancer cells and may explain the protective signals observed with neuraxial anaesthesia; which when used in addition or as an alternative to general anaesthesia, reduces circulating catecholamine levels, inflammation, immunosuppression, and provides an alternative means of achieving sympathetic blockade during cancer surgery, inflammation, and immunosuppression. Overall, the conclusions of two meta-analyses of predominantly retrospective data published in the past 3 years show that the use of perioperative neuraxial anaesthesia is associated with a survival benefit.[29, 30] However, robust studies of neuraxial technique on cancer outcomes are awaited.

RIOT:

While we continue to work on basic and translational science projects to better understand the perioperative biology in the context of cancer care and await definitive clinical trials of preferential anaesthetic techniques for cancer surgery, our aim and efforts should also focus on optimizing the patient's preoperative condition (prehabilitation) to ensure the maximum benefits of surgery (neoadjuvant therapy when indicated, nutritional enhancement, physiological conditioning [strength and cardiovascular training], anaemia management, and behavioral therapy for stress reduction) to minimize postoperative complications and get the patient 'back on track' to complete their cancer journey (adjuvant therapies).

Within the perioperative care of cancer patients, the term "RIOT" is used to describe a surgical oncology quality metric for Return to Intended Oncologic Therapy. This simple formula divides the number of patients who initiated postoperative adjuvant therapy (can be surgical, medical, or radiotherapy) by the number intended to receive it based on stage of cancer to create the RIOT rate. Various adjuvant systemic chemotherapy trials give a glimpse of these data. Initial exploration of these metrics determined that failure to RIOT was associated with significantly worse oncologic outcomes.[31] These findings have received subsequent support by several groups studying outcomes in a number of different cancers.[32, 33] As such it is increasingly suggested that all surgeons who perform cancer surgery, be able to quote/report their RIOT metrics. Further, RIOT may be a reliable surrogate endpoint for recurrence-free and overall survival, available early in the cancer care continuum.

In summary, effective perioperative care of the cancer patient is increasingly complex and our knowledge of the biologic impact of the adrenergic-inflammatory-immune (surgical) stress response and anaesthetic techniques on cancer progression pathways, and thus long-term outcomes, is rapidly expanding. As such, anaesthesia and perioperative care for cancer patients should not simply be the prevention of awareness and administration of analgesia but rather an opportunity to minimise the biological perturbation of the surgical stress response and to adjust anaesthetic techniques to minimize activation of cancer progression pathways. Importantly, we should also focus our perioperative strategies on

reducing perioperative morbidity to ensure functional recovery after surgery that allows timely return to intended oncologic (adjuvant) therapies (RIOT).

It is this comprehensive approach to patient care that could potentially influence oncological outcomes by minimizing loco-regional recurrence and distant metastasis.

References

1. Alkire BC, Shrime MG, Dare AJ, Vincent JR, Meara JG. Global economic consequences of selected surgical diseases: a modelling study. *The Lancet Global health* 2015; **3 Suppl 2**: S21-7.
2. Sullivan R, Alatise OI, Anderson BO, et al. Global cancer surgery: delivering safe, affordable, and timely cancer surgery. *The Lancet Oncology* 2015; **16**(11): 1193-224.
3. Seyfried TN, Huysentruyt LC. On the origin of cancer metastasis. *Critical reviews in oncogenesis* 2013; **18**(1-2): 43-73.
4. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. *Nature reviews Clinical oncology* 2017.
5. Markovic SN, Knight PR, Murasko DM. Inhibition of interferon stimulation of natural killer cell activity in mice anesthetized with halothane or isoflurane. *Anesthesiology* 1993; **78**(4): 700-6.
6. Lu Y, Wang J, Yan J, et al. Sevoflurane attenuate hypoxia-induced VEGF level in tongue squamous cell carcinoma cell by upregulating the DNA methylation states of the promoter region. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* 2015; **71**: 139-45.
7. Dubowitz JA, Sloan EK, Riedel BJ. Implicating anaesthesia and the perioperative period in cancer recurrence and metastasis. *Clinical & experimental metastasis* 2017.
8. Chen RM, Chen TG, Chen TL, et al. Anti-inflammatory and antioxidative effects of propofol on lipopolysaccharide-activated macrophages. *Annals of the New York Academy of Sciences* 2005; **1042**: 262-71.
9. Chamaraux-Tran TN, Piegeler T. The Amide Local Anesthetic Lidocaine in Cancer Surgery-Potential Antimetastatic Effects and Preservation of Immune Cell Function? A Narrative Review. *Frontiers in medicine* 2017; **4**: 235.
10. Ramirez MF, Tran P, Cata JP. The effect of clinically therapeutic plasma concentrations of lidocaine on natural killer cell cytotoxicity. *Regional anesthesia and pain medicine* 2015; **40**(1): 43-8.
11. Dunn LK, Durieux ME. Perioperative Use of Intravenous Lidocaine. *Anesthesiology* 2017; **126**(4): 729-37.
12. Soltanizadeh S, Degett TH, Gogenur I. Outcomes of cancer surgery after inhalational and intravenous anesthesia: A systematic review. *Journal of clinical anesthesia* 2017; **42**: 19-25.
13. Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The choice of anaesthetic--sevoflurane or propofol--and outcome from cancer surgery: a retrospective analysis. *Upsala journal of medical sciences* 2014; **119**(3): 251-61.
14. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: a retrospective study. *Korean journal of anesthesiology* 2016; **69**(2): 126-32.
15. Wigmore TJ, Mohammed K, Jhanji S. Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology* 2016; **124**(1): 69-79.
16. Zheng X, Wang Y, Dong L, et al. Effects of propofol-based total intravenous anesthesia on gastric cancer: a retrospective study. *OncoTargets and therapy* 2018; **11**: 1141-8.
17. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study. *British journal of anaesthesia* 2014; **113 Suppl 1**: i56-62.
18. Jaura AI, Flood G, Gallagher HC, Buggy DJ. Differential effects of serum from patients administered distinct anaesthetic techniques on apoptosis in breast cancer cells in vitro: a pilot study. *British journal of anaesthesia* 2014; **113 Suppl 1**: i63-7.
19. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. *BJA Education* 2016; **16**(9): 292-8.
20. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology* 2000; **93**(3): 858-75.
21. Kim MP, Park SI, Kopetz S, Gallick GE. Src family kinases as mediators of endothelial permeability: effects on inflammation and metastasis. *Cell and tissue research* 2009; **335**(1): 249-59.
22. Kobayashi H, Boelte KC, Lin PC. Endothelial cell adhesion molecules and cancer progression. *Current medicinal chemistry* 2007; **14**(4): 377-86.
23. Baptista-Hon DT, Robertson FM, Robertson GB, et al. Potent inhibition by ropivacaine of metastatic colon cancer SW620 cell invasion and NaV1.5 channel function. *British journal of anaesthesia* 2014; **113 Suppl 1**: i39-i48.
24. Lenglet S, Mach F, Montecucco F. Matrix metalloproteinase-9: a deleterious link between hepatic ischemia-reperfusion and colorectal cancer. *World journal of gastroenterology* 2012; **18**(48): 7131-3.
25. Wang HL, Yan HD, Liu YY, et al. Intraoperative intravenous lidocaine exerts a protective effect on cell-mediated immunity in patients undergoing radical hysterectomy. *Molecular medicine reports* 2015; **12**(5): 7039-44.
26. Pantziarka P, Bouche G, Sullivan R, Ilbawi AM, Dare AJ, Meheus L. Perioperative therapies - Enhancing the impact of cancer surgery with repurposed drugs. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2017; **43**(11): 1985-8.
27. Shaashua L, Shabat-Simon M, Haldar R, et al. Perioperative COX-2 and beta-Adrenergic Blockade Improves Metastatic Biomarkers in Breast Cancer Patients in a Phase-II Randomized Trial. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2017; **23**(16): 4651-61.
28. Zhou L, Li Y, Li X, et al. Propranolol Attenuates Surgical Stress-Induced Elevation of the Regulatory T Cell Response in Patients Undergoing Radical Mastectomy. *Journal of immunology* 2016; **196**(8): 3460-9.

29. Sun Y, Li T, Gan TJ. The Effects of Perioperative Regional Anesthesia and Analgesia on Cancer Recurrence and Survival After Oncology Surgery: A Systematic Review and Meta-Analysis. *Regional anesthesia and pain medicine* 2015; **40**(5): 589-98.
30. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery: an updated meta-analysis. *Oncotarget* 2016; **7**(12): 15262-73.
31. Aloia TA, Zimmitti G, Conrad C, Gottumukalla V, Kopetz S, Vauthey JN. Return to intended oncologic treatment (RIOT): a novel metric for evaluating the quality of oncosurgical therapy for malignancy. *Journal of surgical oncology* 2014; **110**(2): 107-14.
32. Merkow RP, Bilimoria KY, Tomlinson JS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Annals of surgery* 2014; **260**(2): 372-7.
33. Slankamenac K, Slankamenac M, Schlegel A, et al. Impact of postoperative complications on readmission and long-term survival in patients following surgery for colorectal cancer. *International journal of colorectal disease* 2017; **32**(6): 805-11.