

# Onco-Anaesthesia: Can we make a difference?

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### Overview

The global burden of disease is changing at a rapid pace, with an exponential increase in the incidence of cancer, obesity and age-related morbidity. The World Health Organisation (WHO) predicts 22 million new cancer diagnoses per year globally by 2030. Of the current 15.2 million new cases of cancer (2015) an estimated 60-80% of cases will need surgery, some several times, for diagnostic, therapeutic, or palliative reasons.

It is increasingly recognized that anaesthetists have the opportunity to positively influence oncological outcomes, with potential for disease modification. This lecture will explore our current understanding of how the biological perturbations (neural-inflammatory-immunomodulating stress responses) that accompany surgery and how anaesthetic technique impact the susceptibility to perioperative tumor spread, including activation of micrometastatic disease. These pathophysiological processes impact tumour-stromal interaction, immune-editing, and genotypic plasticity and can be modulated by our choice of anaesthetic techniques, which include anaesthetic agents (e.g. volatiles [which are immunogenic], TIVA [which may have anti-inflammatory properties], neuraxial techniques [which block the adrenergic system]) and perioperative adjuncts (e.g. opioids, NSAIDs,  $\beta$ -blockers [which are anti-adrenergic and anti-inflammatory]). Whilst much of our understanding of these potential interactions comes from either in vitro cell line or xenograft models, there is increasing clinical data (albeit predominantly retrospective in nature) demonstrating an association with improved long-term survival for anaesthesia techniques that are underpinned by an anti-adrenergic-anti-inflammatory strategy. Until such time as adequately powered, randomized, controlled trials confirm or refute these findings we should place emphasis on such a strategy, which is easily delivered within our current armamentarium of regional (neuraxial) and intravenous anaesthetic techniques.

Additionally, it is recognized that postoperative morbidity negatively impacts on the ability of patients to return to their intended oncological treatment (RIOT; the cancer journey - with postoperative adjuvant therapy) with reduced cancer survival. As such, our focus should be on a comprehensive approach to patient care to facilitate optimal surgical outcomes, thereby ensuring timely access to such adjuvant therapies to potentially improve oncological outcomes by minimizing loco-regional recurrence and distant metastasis. Sedentary lifestyle choices, comorbid disease, and neoadjuvant cancer treatments adversely impact on the physiologic capacity (fitness) of patients, which increases postoperative morbidity. Well-coordinated perioperative care plans with optimization of co-existing diseases, prehabilitation with exercise, haematinic and nutritional optimization, implementation of evidence-based and outcome driven perioperative care pathways, a thorough understanding of the potential impact of anaesthetic technique on cancer biology, intensive postoperative surveillance to ensure early rescue from postoperative complications, and aggressive treatment of recurrent cancer are integral to achieving better cancer outcomes.

### *Discussion*

The global burden of disease is changing at a rapid pace, with an exponential increase in the incidence of cancer, obesity and age-related morbidity. Cancer is currently the leading cause of death in developing nations and ranks next to cardiovascular diseases as the most common cause of death in the developed world. The WHO predicts that there will be 22 million new diagnoses of cancer per year globally by 2030. For many cancers, a diagnosis is no longer a terminal disease, but rather considered a chronic medical condition, often requiring increasingly complex surgical procedures with a curative intent. Of the 15.2 million new cases of cancer in 2015, an estimated 80% of cases will need surgery, some several times.<sup>1</sup> For the

majority of patients with solid organ tumors, surgical resection still remains the cornerstone of intervention for both curative as well as palliative measures. As such, as perioperative clinicians anaesthetists have an important role if effectively managing this global cancer 'tsunami'.

Surgery is a cost-effective intervention in terms of adjusted quality of life years gained by the patients. Importantly, lack of timely surgical access is estimated to equate to total welfare loss of ~17% of gross domestic product (GDP), with cancer and trauma accounting for more than 95% of macroeconomic loss in developing countries.<sup>2</sup> Improvements in early detection and effective new cancer treatment modalities will lead to a significant increase in the numbers of cancer survivors who will continue to need perioperative services for care of their primary tumors, disease recurrence, and non-oncological surgical care. As such, building surgical capacity should be a global health priority, with an urgent need for an improved understanding of the perioperative needs of the cancer surgery population and a thorough understanding of the implications of the biology of the disease process and cancer therapies on perioperative care and vice versa to ensure further improvement in cancer outcomes.

Within the 21<sup>st</sup> century a model of comprehensive cancer care, which is research driven, has resulted in lower rates of perioperative morbidity and mortality and improved oncological outcomes for a variety of solid tumours reported by high-volume centres.<sup>3-8</sup> This benefit extends into long-term survival, with a significantly greater 5-year survival benefit from high-volume centres for oesophageal cancer surgery, with significant but lesser benefit also reported in gastric, pancreatic, and lung cancers. This observed correlation between hospital volume and late survival after cancer surgery is best explained by the differences in the quality of the initial surgery (including lymph node dissection and margin free resection) performed by high-volume and/or subspecialty trained surgeons and within the setting of an integrated multidisciplinary network of expertise, including medical oncology, pathology and radiology, anaesthesiology, perioperative and critical care medicine, and allied health services. Well-coordinated perioperative care plans with better optimization of co-existing diseases, implementation of evidence-based and outcome driven perioperative care pathways, a thorough understanding of the impact of anaesthetic agents on cancer biology, intensive postoperative surveillance with early rescue from postoperative complications,<sup>9,10</sup> and aggressive treatment of recurrent cancer are integral to achieving better outcomes. Cancer patients and survivors present with increasingly complex medical co-morbidities, age-related conditions, disease specific challenges, including underlying causative risk factors, location of tumour, and side effects of increasingly complex cancer therapies (chemotherapy, immunotherapy and radiotherapy) with consequent alteration of local and distant organ function. In addition, our understanding of how the biological perturbations that accompany the perioperative surgical stress response and how our anaesthetic techniques impact susceptibility to perioperative tumor spread and control is rapidly evolving. As such, it is increasingly recognized that perioperative clinicians have the opportunity to positively influence oncological outcomes for cancer patients, with accumulating evidence for potential disease modification dependent upon anaesthetic technique and management of the perioperative period.<sup>12-15</sup>

Significant advances have been made with regards to understanding the pathophysiological processes (neural-inflammatory-immunomodulating stress response) of the perioperative period and their effects on tumour-stromal interaction, immune-editing, and genotypic plasticity and how we can modulate these effects within our current armamentarium of anaesthetic techniques, including anaesthetic agents (e.g. volatiles, TIVA, neuraxial techniques) and perioperative adjuncts (e.g. opioids, NSAIDs,  $\beta$ -blockers).<sup>12-18</sup> Furthermore, cancer treatments can impair the physiologic reserve (functional capacity; fitness) of patients,<sup>19,20</sup> with significant impact on the ability of patients to withstand surgery without morbidity.<sup>21,22</sup> The ability to optimise patients to ensure optimal postoperative outcome is underpinned by the subsequent adverse impact of postoperative morbidity on the ability of patients to return to their intended oncological treatment (RIOT; postoperative adjuvant therapies) and the cancer care journey.<sup>15,23</sup> Therefore, an in-depth knowledge of the adverse effects and toxicities associated with cancer therapies (chemotherapeutic agents, immunotherapy and radiotherapy) on the patient's overall functional status and timing of the surgical intervention to offer the patient the best chance for cancer control or cure is crucial. While we continue to undertake basic and translational research to better understand the perioperative biology in

the context of cancer care, our aim and efforts should be focused 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 response reduction), minimize postoperative complications, and ensuring that the patient remains 'on track' to complete their cancer journey (adjuvant therapies).<sup>24,25</sup>

Currently there are no prospective randomized controlled studies, which offer clear benefits of one anaesthetic technique (or perioperative strategy) over the other in terms of recurrence free survival or overall survival after cancer surgery. Published retrospective studies offer contradictory results and most of the studies have not taken the oncological factors (tumor stage and type, tumor burden, lympho-vascular space invasion, response to therapy, etc.), nutritional state, inflammatory burden and functional status into account.<sup>28</sup> Furthermore, one has to acknowledge the known shortcomings (bias in treatment allocation to the study groups) of a retrospective study despite the strengths of the clinical end points. In-vitro and animal data similarly cannot be correlated with or translated to clinical experience although they form the basis for future research models and can guide appropriate clinical protocols. Published literature from in-vitro and animal models usually involves studying the effects of individual cell lines in a controlled environment. We now also understand that the cancer biology for each of the tumors is different, and also that within each tumor there is phenotypic and genotypic heterogeneity and plasticity that explains the differences in response to therapy amongst individual patients and also the existence of circulating tumour cells (CTCs) often exacerbated by surgery.<sup>26,27</sup> Our growing understanding of the concept of CTC release during surgery offers one possible explanation for the tenacity of some of the tumors in escaping the innate immunity of the host, with potential activation of the distant microenvironment for CTCs and that of undetected micrometastatic disease by the biologic perturbation that accompanies the perioperative surgical stress response. This potentially leads to loco-regional disease and distant clinical metastasis years after the primary therapeutic interventions with curative intent. This may explain the bimodal recurrence pattern observed after breast cancer surgery that is positively impacted in observational studies by perioperative NSAIDs.<sup>28-31</sup>

To optimally care for the cancer surgery population, we need hypothesis driven protocols to evaluate if indeed these strategies are efficacious in improving long-term cancer outcomes. However, we should also marry lean methodology in our processes of care, with enhanced recovery programs that incorporate clinical strategies that target biologically plausible mechanisms (e.g. neural-inflammatory-immunomodulation) that may drive cancer recurrence to ensure optimal oncological outcomes. In the complex perioperative space, where key interventions to influence outcomes are frequently multimodal it will be difficult to show the efficacy of any one intervention (anti-adrenergic, anti-inflammatory strategies, avoiding volatile anesthesia, opioid-sparing strategies, goal directed fluid therapy and hemodynamic optimization, minimizing oxygen debt, etc.) singularly or as a unimodal intervention. It is therefore vital for anaesthetists and perioperative clinicians to collaborate with specialists in all areas of cancer care delivery (medical oncologists, immunologists, radiation oncologists, surgical oncologists, intensive care physicians, integrative medicine clinicians, and internal medicine physicians).

Contemporary surgical practice strategies focus on preoperative and perioperative optimisation to combat the morbidity inflicted by cancers and their treatments. Examples of these include prehabilitation with high protein nutrition, and exercise regimes to facilitate recovery from deconditioning associated with neoadjuvant therapies.<sup>24</sup> Some of this work has been incorporated into enhanced recovery packages, where opportunity presents for perioperative clinicians to be key advocates in initiating lifestyle changes in cancer patients—smoking cessation, exercise, and initiating discussions on advance care planning (ACP).

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. More importantly, we should focus our perioperative strategies on reducing perioperative morbidity to ensure functional recovery after surgery that allows timely return to intended oncologic (adjuvant) therapies (RIOT).<sup>23</sup> It is this comprehensive approach to patient care that could potentially influence oncological outcomes by minimizing loco-regional recurrence and distant metastasis. We require an ongoing concerted effort by scientists and clinicians, with focused research to improve our understanding of the impact of anaesthetic and perioperative strategies on long-term cancer outcomes to effectively confront the global cancer 'tsunami'.

### Recommended Reading

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