

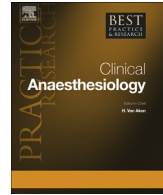


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Challenges in research related to perioperative cancer care and cancer outcomes



Juan P. Cata, MD., Assistant Professor ^{a,*},
Andrea Kurz, MD., Professor, Vice Chair ^{b,1}

^a Department of Anaesthesiology and Perioperative Medicine, The University of Texas – MD Anderson Cancer Center, Houston, TX, USA

^b Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

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Surgery is one of the most commonly used treatments to attempt cure of early-stage and some late-stage solid tumours. Paradoxically, surgery itself and some of the medical interventions involved in the perioperative care of cancer patients may be associated with an increased chance of metastasis. Researchers and perioperative clinicians have studied the phenomenon of surgery-induced immunosuppression and postoperative cancer recurrence for several decades. Unfortunately, the translation of basic science research into human studies is not clear. Moreover, a recent proliferation of retrospective studies with conflicting results and significant limitations has not shed light on the understanding of whether regional anaesthesia, anti-inflammatory interventions or blockade of the sympathetic response improve survival after cancer surgery. Ultimately, randomised controlled trials are required to answer some of the questions raised by preclinical and retrospective studies; however, investigators face many challenges in conducting these trials. Unless sufficient funding is obtained and cooperative research is developed in the near future, clinicians will not know whether anticancer perioperative interventions are useful to improve cancer-related survivals.

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* Corresponding author. Tel.: +1 713 792 4582.

E-mail addresses: jcata@mdanderson.org (J.P. Cata), ak@or.org (A. Kurz).

¹ Tel.: +1 713 445 9924.

Introduction

Cancer is a major health problem worldwide. Recent epidemiological data indicate that approximately 40% of men and women have a chance to develop invasive cancers from the moment of birth to death [1]. Hence, millions of patients worldwide will face the diagnosis of cancer every year. Importantly, the five most prevalent cancers in the adult population (prostate, breast, lung, colorectal and bladder cancer) are amenable to surgical resection when detected timely [1]. As a result, the number of surgical interventions targeted to cure or palliate different cancers will increase in the near future [2].

For more than two decades, investigators have tried to answer the question of whether perioperative interventions such as surgery itself, anaesthetics, analgesics, beta-blockers, anti-inflammatory drugs and blood transfusions have an impact on cancer biology [4,5]. The results of primarily basic science studies indicate that surgical stress, volatile anaesthetics and analgesics enhance the ability of cancer cells to proliferate and invade because of their direct stimulating effects on those cells, immunosuppressive effects and pro-angiogenic actions [6–10]. Based on these premises, clinical researchers have tried to answer the question of whether perioperative medical interventions affect oncological outcomes. Most of these studies were relatively small and retrospective, leading to conflicting results. Hence, no clear conclusions can be drawn from the current evidence on whether alterations in perioperative care might change long-term outcomes in patients undergoing cancer surgery.

In this chapter, we present the advantages, limitations and challenges of conducting clinical trials that might help to elucidate the important question of whether or not perioperative interventions may influence long-term oncological outcomes.

Basic science and translational studies

A wide variety of *in vitro* and *in vivo* animal experiments have been used to test the effects of anaesthetics, analgesics and surgical stress-response mediators on the innate and adaptive immune system. Most studies agree that volatile anaesthetics, opioids and barbiturates are depressants of the immune response against cancer. These studies also suggest that amelioration of the surgical stress and inflammatory response through regional anaesthesia and blockade of the beta-adrenergic receptors and anti-inflammatory agents is associated with reduced metastasis formation [6–8,11–17].

Unfortunately, the translation of this research into humans appears to be far from clear. A series of elegant randomised controlled studies in breast cancer patients demonstrate that the use of regional anaesthesia causes a reduction in circulating metalloproteinases, interleukin-1 and vascular endothelial growth factor [18,19]. Although these effects indicate a reduction in the inflammatory response and potential protection of the immune system, the actual impact of regional anaesthesia on metastasis formation was not tested. To complicate this matter further, the use of regional anaesthesia was not effective in preventing the suppression in cell-mediated cytotoxicity observed in patients undergoing lung cancer and abdominal surgery [20–22].

In summary, the data originated from basic science research are promising in terms of the use of immune-protective techniques for cancer surgery. However, the results of studies conducted in 'real world' clinical situations are conflicting.

Retrospective and population database studies: the good, the bad and the ugly

The use of perioperative databases to assess the effectiveness of interventions in 'real clinical practice' has grown considerably in recent years due to advances in data capture (i.e., electronic medical records and electronic registries), data integration and statistical analysis [23]. However, the use of databases to conduct outcomes research has advantages and disadvantages.

The advantages of database research are the relative low cost of maintenance and ease of integration with other sources. However, it is important to remember that technical support and personnel in charge of 'cleaning and mining' databases may be expensive when the data are gathered from non-research-oriented medical information systems [24]. The use of databases for research has

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