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Editorial

Cancer Recurrence and Anesthetic Technique: A "Wake Up Call"

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While the definitive treatment for cancer is frequently surgery, the perioperative period represents one of the greatest risk factors for tumor cell proliferation and eventual metastases [1-3]. Several studies have demonstrated that surgery stimulates neuroendocrine and cytokine stress responses, suppresses cell-mediated immunity, disperses tumor cell emboli, and promotes tumor growth and metastasis in animal models [4-6]. As anesthesiologists and pain specialists, we may be no less responsible for the recurrence of cancer and the long-term outcome of oncologic patients than our surgical colleagues. Several retrospective studies have recently evaluated the impact of anesthetic technique on cancer recurrence following oncologic surgery.

Since 2006, fifteen retrospective articles have been published that examine the effect of regional anesthesia on rates of cancer recurrence. Results have ranged from a 4-fold decrease in postoperative metastases [7] for mastectomies that received preoperative paravertebral neural blockade, to no significant difference in overall survival following lymph node dissection for malignant melanoma under neuraxial anesthesia [8]. While the majority of findings indicate a potential benefit for regional anesthesia in oncologic patients, they also highlight the disparate effect of anesthetic technique on different cancer types.

The exact mechanism by which anesthetic techniques impact cancer recurrence is still under investigation; however, modulation of cell-mediated immunity has been identified in several in-vitro models [9,10]. Intraoperatively, cytokines such as IL-2, IL-12, and IFN-y are suppressed. As a result, the number of circulating natural killer (NK) cells, cytotoxic T-lymphocytes, and the ratio of T-helper 1 to T-helper 2 are significantly reduced. This immunosuppression effectively inhibits the body's natural ability to defend against malignancy and dispersed tumor emboli during surgery. By lowering plasma levels of cortisol and catecholamines, however, intraoperative use of regional anesthesia reduces the immunosuppression caused by surgical stimulation and thereby helps maintain NK function and cellular immunity.

Propofol and local anesthetics have also been shown, on a cellular level, to inhibit tumor growth and progression. In mice, Kushida et al., have reported that propofol promotes cytotoxic T-lymphocyte activity and inhibits lymphoma growth. In another study, Propofol decreased extracellular matrix protein expression and subsequent colon cancer cell invasiveness [11,12]. Local anesthetics, on the other hand, appear to act through the voltage-gated sodium channels (VGSCs) expressed by tumor cells and thereby inhibit metastasis [13-15], cell proliferation [16], and Src signaling-mediated cancer cell migration [17]. These benefits, however, are dependent on the degree to which tumor cells express VGSCs, and not all cancers express these receptors.

While the available clinical evidence suggests a protective effect for regional anesthesia, local anesthetics and propofol, it presents contrary results for inhalational and intravenous anesthetics as well as opioids. Both general anesthetics and opioids are immunosuppressive and thereby render patients more susceptible to tumor progression [6-18,19]. Few studies, however, have directly evaluated the effect of inhalational anesthetics on tumor recurrence. Kawaraguchi et al., for example, found that isofluorane protects cancer cells from tumor necrosis factor (TNF)-induced apoptosis [19]. More research has been conducted on the impact of opioid use in cancer recurrence. In addition to immunosuppression, narcotics have been shown to promote tumor growth via induced angiogenesis [20] and cytoskeletal regulation in some types of breast adenocarcinoma cells [21], thereby facilitating tumor migration and growth. While the available evidence is compelling, prospective clinical trials are scarce, and most data comes from animal and in-vitro studies.

As of 2013, only one major prospective randomized-control clinical trial has been published on the long-term impact of anesthetic technique and postoperative cancer recurrence. The MASTER trial was a multicenter prospective clinical study which randomized oncologic patients undergoing major abdominal surgery to receive general anesthesia with either epidural or opioid analgesia. No significant difference was detected in cancer-free survival [22]. Unfortunately, the amount of volatile anesthetic

was not recorded and may represent a significant confounding variable. Smaller prospective studies have also been conducted, but like the MASTER trial, they also suffer from the difficulty associated with multimodal anesthesia and the ability of these studies to eliminate confounders and determine the contribution of each individual anesthetic factor to cancer recurrence. Despite the growing body of animal and laboratory evidence, controlled clinical trials are desperately needed to evaluate the impact of each individual anesthetic on cancer recurrence and long-term patient survival. Three multi-center prospective RCTs are on the horizon, however. These trials, looking at tumor recurrence and anesthetic technique for breast, lung, and colon cancers are being conducted by the Cleveland Clinic, Mater University Hospital, and the University of Dusseldorf. Results are expected to be reported in 2015, 2018, and 2022 [6]. Meanwhile, our patients and anesthesia providers have to wait. Unfortunately, some of our patients do not have the luxury of time.

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