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Editorial

The effects of anesthetic and analgesic techniques on immune function

Cancer is a leading cause of morbidity and mortality worldwide, despite the continued development of new medical and surgical strategies to combat the disease. In the United States (U.S.), mortality rates for all cancers were reported at 178.7 per 100,000 population (age-adjusted) for the period 2005–2009 [1]. In 2008, Cancer Research U.K. estimated that there were just over two million people living with or after cancer in the U.K. and this incidence was predicted to rise by more than 3% per year [2].

The management strategy for a number of cancers involves surgical resection of a primary tumor (with or without neoadjuvant or adjuvant chemotherapy or radiation treatment). With this increase in the number of patients with cancer, anesthesiologists will be tasked with managing these patients to a greater degree. There is, however, an evolving opinion in the literature that a number of perioperative factors may directly affect cancer cells and also affect the development of metastases [3,4]. This has potentially significant implications for our speciality.

Perioperative factors which could potentially influence cancer recurrence and metastasis include surgery *per se*, pain, volatile anesthesia, propofol, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), allogeneic blood transfusion, psychological stress, hypothermia, and regional anesthesia. These factors all influence the immune system and are discussed in a recent review by Heaney et al [5]. Cell-mediated immunity in particular forms the primary defense against tumor cells, one of its main components being natural killer (NK) cells. There is an association between stress-induced attenuation of NK cell activity and the promotion of breast tumor growth and metastases in an animal model [6], and patients with low levels of NK cells may be at risk of developing cancer, or metastasis after cancer surgery [7].

Regional anesthesia has been postulated to have an effect on cancer outcome. These studies have been positive [8–14] and negative [15–19]. However, they are mainly retrospective in design. A recent meta-analysis of the effect of central neuraxial regional anesthesia compared with general anesthesia on postoperative NK cell function demonstrated no significant difference between the two groups [20]. However, the studies were heterogeneous with large-scale, prospective studies lacking.

Further translational data regarding the effect of regional anesthesia on cancer is presented by Cata et al in the current issue of the *Journal of Clinical Anesthesia* [21]. This is a relatively small study, conducted in a single center in the U.S., which examined perioperative immune function in the context of thoracic surgical resection of non-small cell lung cancer. The authors investigated the acute changes in the percentage and function of NK cells and the percentage of NK T cells, T helper cells, and T cytotoxic lymphocytes in patients with non-small cell lung cancer before and after surgery during general anesthesia and postoperative thoracic epidural analgesia. They also examined preoperative and postoperative plasma concentrations of TH1 cytokines (IL-2 and IFN-γ) and a TH2 cytokine (IL-4).

The authors found that the percentage and function of NK cells was significantly decreased after surgery in all lung cancer patients who were evaluated, but the percentage of NK cells, T helper cells, and cytotoxic T lymphocytes remained unchanged postoperatively. The postoperative plasma concentration of the three measured cytokines was similar to preoperative levels; hence, there was no perioperative change in the TH1/TH2 ratio. The authors concluded that innate immunity is depressed in patients with non-small cell lung cancer after surgical resection, and immunity is not preserved by the use of postoperative epidural analgesia.

This study is not without its limitations, most notably its single-center design and the possible selection bias of the cohort. Also, the measurement of only three cytokines rather limits the ability to interpret the findings. Perhaps consideration should have been given to structuring the study (even in a *post hoc* fashion) as an epidural versus opioid analgesia study. The use of intraoperative opioids and postoperative epidural analgesia would seem to introduce a confounder to the study's findings. The conclusions are therefore somewhat overstated. Nevertheless, the authors are to be congratulated for conducting this interesting and well-designed study.

The fervent discussion regarding the effects of anesthetic and analgesic techniques on immune function continues

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unabated, not least because what exactly constitutes "immune fuction" *per se* is unclear. Clinically relevant endpoints are required, as are large-scale prospective trials to examine these endpoints – some of these are currently underway (NCT00418457 [22], NCT011799308, NCT00684229) with estimated completion dates of March 2015, August 2018, and December 2022, respectively. If indeed there are significant effects on patient outcome from anesthetic technique, we have a duty to examine them in a scientifically thorough manner – our patients expect nothing less.

Ian Conrick-Martin FCAI, MRCPI, FJFICMI
(Specialist Registrar in Anaesthesia)
Department of Anaesthesia
Mater Misericordiae University Hospital
Dublin 7, Ireland
E-mail address: iancm25@hotmail.com

Donal J. Buggy MD, FRCPI, FRCACSI, FRCA
(Honorary Senior Lecturer in Anaesthesia)
Department of Anaesthesia
Mater Misericordiae University Hospital
Dublin 7, Ireland
Outcomes Research Consortium
Cleveland Clinic Foundation
Cleveland, OH 44195, USA

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