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EDITORIAL

Special issue on anaesthesia and cancer

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The hypothesis that anaesthetic and analgesic technique during cancer surgery affects recurrence or metastasis was first proposed in 2006[1] and has since become one of the most important research questions in the speciality, as confirmed in a recent research priority setting exercise.[2]

Building on the success of the inaugural *BJA* Workshop on Anaesthetic Neurotoxicity and Neuroplasticity held in Salzburg in 2012, which lead to a Special Online Issue of *BJA*, a group of researchers with a proven publication track record in the field of anaesthesia and cancer recurrence and metastasis convened in the College of Anaesthetists of Ireland in Dublin (see cover image) on May 29–30, 2013, for the *BJA* Dublin Research Workshop on Anaesthesia and Analgesia in Cancer. This 2 day meeting, sponsored by *BJA*, was organized to review and critically assess currently available evidence from experimental cell culture models and live animal models, together with translational and clinical studies, and to identify priorities for future research directions. Organized by D.J.B. (Dublin), it convened more than 20 clinician investigators in anaesthesia, oncology, immunology, and opioid pharmacologists from around the world for an intensive series of lectures and discussions. The result is this *BJA* Special Issue on Anaesthesia and Cancer, a collection of cutting-edge original investigations from the delegates and other investigators who submitted papers following a call for manuscripts from *BJA*. Like the inaugural Special Issue on Neurotoxicity, this themed issue is again presented in open access format via the *BJA* website (http://bja.oxfordjournals.org), which confirms the journal's commitment to supporting topical research and facilitating its free rapid dissemination online.

It consists of 13 original investigations and a short overview encompassing a consensus statement.[3] A systematic review of this subject was published recently.[4]

The original manuscripts may be classified as investigations of direct effects of anaesthetic and analgesic drugs on cancer cell biology (5), translational studies on the effect of anaesthetic technique in randomized cancer surgery patients on perioperative host immunity and cancer metastatic function (3), and new retrospective clinical data on perioperative factors associated with subsequent recurrence or metastasis (6).

The section on direct effects of anaesthetic–analgesic drugs on cancer biology is ignited by J. Nguyen, K. Luk, and colleagues, with an elegant series of live animal experiments using a transgenic mouse model of breast cancer. These mice, programmed to develop breast tumours, were treated at different ages with clinically relevant doses of morphine to determine the effect on tumour development and animal survival. While morphine was absolved of instigating tumour development, it clearly enhanced progression of established tumours, mediated by tumour expression of μ-opioid receptors (MOR).[5] Ash and colleagues[6] undertook novel work on the anaesthetic gas xenon in breast cancer cells and found that in contrast to sevoflurane, it inhibits breast cancer cell migration by an *N*-methyl-D-aspartate receptor-mediated mechanism, and decreased release of the angiogenesis factor RANTES in oestrogen receptor-negative breast cancer cells. Afsharimani and colleagues[7] co-cultured breast cancer cells with macrophages or endothelial cells to study the effect of non-steroidal anti-inflammatory drugs (NSAIDs) and antifibrinolytic agents on extracellular membrane proteases which regulate the tumour microenvironment, and found mixed results, which warrant further investigation in animal and clinical studies.

There has been great interest in recent cell culture data suggesting inhibitory effects of amide local anaesthetics on cancer cell function, which is progressed here by Lirk and colleagues,[8]

who show that lidocaine and ropivacaine, but not racemic bupivacaine, have demethylating effects on DNA of cancer cells, and this effect is enhanced when lidocaine is combined with a specific chemotherapy demethylating agent, suggesting novel potential future therapeutic strategies in perioperative cancer management. Consistent with these findings, D.T. Baptista-Hon and T. Hales' group demonstrate that ropivacaine inhibits variants of voltage-activated Na^+ channels, which are expressed by metastatic cancer cells, and that it duly inhibits these cells' malignant invasion.[9]

Fascinating translational studies on the effect of anaesthetic technique in randomized cancer surgery patients on perioperative host immunity and cancer metastatic function indicate that epidural regional anaesthesia decreases expression of angiogenesis promoting factors in colon cancer patients.[10] Prior live animal inoculation models of breast cancer suggested a crucial role for Natural Killer (NK) immune cells in resisting perioperative metastasis. Buckley and colleagues[11] focused on the effect of serum of breast cancer patients randomized to receive propofol–paravertebral or sevoflurane–opioid anaesthetic technique on healthy NK cell cytotoxicity against breast cancer cells found that patients randomized to the latter had reduced NK cell activation and tumour cytotoxicity. Separately, Jaura and colleagues showed that serum from breast cancer women randomized to the propofol–paravertebral causes greater apoptosis than sevoflurane–opioid, suggesting that anaesthetic technique alters the serum milieu to impact cancer cell apoptosis, by an unknown mechanism.[12]

Finally, the section on clinical retrospective studies provides new data on an association between preoperative dexamethasone and metastasis colon cancer from a follow-up analysis of a previous randomized controlled trial,[13] and Meyhoff and colleagues,[14] in a *post hoc* analysis of the PROXI trial involving >1300 patients, found an association between administration of high perioperative inspired oxygen fraction ($F_{I_{O_2}} = 0.8$) and shorter time to onset of new cancer, although the incidence of new cancer was similar among patients randomized to 80% or 30% oxygen.

Intraoperative NSAIDs and a low preoperative neutrophil to lymphocyte ratio were associated with improved outcome in a retrospective analysis of $n>700$ patients undergoing breast cancer surgery.[15] In just 99 patients with non-small-cell lung cancer undergoing laparoscopic thoracotomy surgery, an association was found between higher doses of opioid in the first 4 days after operation and higher metastatic rate at 5 yr.[16] And while there are conflicting reports on the influence of epidural anaesthesia on prostate cancer recurrence in existing studies, a large matched retrospective study of >1600 patients suggested a positive association.[17] Finally, Singleton and colleagues retrospectively analysed lung cancer tissue samples, and found greater MOR expression in lung cancer tissue compared with adjacent normal lung tissue. Furthermore, they observed that a subgroup of patients with known metastatic lung cancer had two-fold greater MOR expression compared with lung cancer patients without metastasis.[18] All of these associations require adequately powered, prospective, randomized controlled trials to prove a causal link, and up to nine such trials are registered on trial databases such as http://www.clinicaltrials.gov.

We hope that this focused compendium of original investigations from researchers in this field will provide the anaesthesia community internationally with a view of the current state-of-art in this area. We thank all contributors to these manuscripts, in addition to Oxford University Press, especially Production Editor Hilary Lamb, the College of Anaesthetists of Ireland for their support of the workshop and *BJA* for its sponsorship.

Declaration of interest

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