The incidence of cancer continues to increase, despite considerable investment in prevention. Additionally, with improved oncological treatments, more people are living with, or being cured of, cancer, and many of these will have disease or treatment-related chronic pain, requiring analgesia. Currently, there is much interest in how analgesics and anaesthetics may impact on cancer biology (especially cancer recurrence and metastases) and consequently on survival. There are at least two areas of particular interest: first, how regional techniques or specific general anaesthetics used for cancer surgery may impact long-term survival, and secondly, how both endogenous and exogenous opioids may modulate cancer biology. It is essential to understand the possible mechanisms of these potential interactions so that patients may be given the best chance of pain-free survival.
How might analgesics or anaesthetics impact on cancer cell biology?

These mechanisms are complex and likely to be multifactorial. Drugs may affect both the immune response and cellular pathways that are key to cancer cell survival and spread both acutely and in the longer term. The host immune system, the tumour itself (including type, stage and site), and the interaction between them are all important in determining cancer outcome. There have been a range of studies on the effects of opioids, local anaesthetics, ketamine, and non-steroidal anti-inflammatory drugs on cell-mediated immunity and/or natural killer cell function, that is, their impact on host defences. They may also affect tumour growth and spread.

It is plausible that the inevitable stress response to primary cancer surgery allied to the transient immune suppression induced by certain anaesthetic agents, or direct effects of these agents on the cancer cells themselves may create conditions conducive to cancer cell survival and spread in the perioperative period.

Furthermore, adjuvant oncological treatment (chemotherapy, radiotherapy, or both) does not occur in the immediate postoperative period, leaving a window of opportunity for micrometastases around the time of surgery to establish and spread. This has led to a focus on perioperative factors that may be modified in order to tip the balance in favour of reduced cancer spread and recurrence. Of particular interest is whether or not regional anaesthesia/analgesia offers advantages over general anaesthesia. Theoretical benefits might include reduced stress response to surgery with consequent reduced adverse effects on immune system responses, optimizing pain control and also potential anti-cancer effects of local anaesthetics themselves.

What is the evidence for outcome after regional anaesthesia in cancer surgery?

A number of retrospective studies of different cancer types have examined the effects of regional anaesthesia, with earlier retrospective work indicating a large effect size in terms of benefit. This area of research was triggered by a retrospective study in breast cancer, suggesting an association between paravertebral anaesthesia and improved disease-free survival. A further study of 225 patients undergoing radical prostatectomy for prostate cancer showed a reduction in biochemical cancer recurrence in the group receiving epidural analgesia, compared with those given systemic opioids with a general anaesthetic.

A secondary analysis of a prospective randomized controlled trial in a similar patient group, with 99 patients, did not find any survival benefit. A follow-up analysis of MASTER trial patients who had colorectal cancer surgery also found no apparent benefit of epidural analgesia compared with systemic opioids in terms of cancer recurrence. Further retrospective studies of surgery for cervical cancer (n=132), ovarian cancer (n=143), and colorectal cancer (n=655) again did not find any major survival benefit, although there did appear to be a benefit from epidural analgesia compared with systemic opioids for patients with the rectal site of disease.

In this issue of the *BJA*, a further retrospective study in patients undergoing surgery for malignant melanoma found a non-significant trend towards improved survival in the spinal anaesthetic group (n=53) compared with the general anaesthetic group (n=221). Both retrospective studies and multicentre studies can be difficult to interpret, as variations in surgical/anaesthetic technique may well influence outcomes. These conflicting findings highlight the urgent need for more prospective research in this area.

There are several recent studies that may help to shed some light on the factors that need further study. A population-based study of more than 42 000 patients undergoing colectomy for cancer (of whom 22% received epidural analgesia) found that 5 yr survival was better in the group who received epidural analgesia compared with ‘traditional pain management’ (which was poorly defined), but found that there was no evidence that epidural use per se decreased the risk of cancer recurrence. One of the separate questions that arises is what factors associated with epidural use are likely to increase survival? In considering this, it is important to take into account the overall ‘package of care’ that makes up the perioperative period, such as using multifactorial protocols to drive early recovery after surgery. These clearly involve teamwork between the anaesthetic, surgical, and ward-based teams, where key components (such as optimal nutrition and fluid management) determining outcome may be factors that are also associated with the use of regional anaesthesia.

There are several possible confounding factors that makes the interpretation of clinical trials to date difficult, including the fact that even when regional techniques were used, opioids were usually given also at some time during the perioperative period either as part of standard care or in cases where neuraxial anaesthesia was inadequate. If, as discussed below, the acute use of opioids may impact on cancer cells, then perhaps future studies should aim to avoid opioids in those patients receiving regional anaesthesia. Further support for this comes from a small randomized controlled trial (n=22) of patients undergoing breast cancer surgery. This study found that the serum of those patients receiving a local anaesthetic paravertebral block plus propofol showed lower proliferation of a breast cancer cell line than patients receiving sevoflurane and an opioid, although cancer cell migration was not different.

There is no doubt that opioids are good analgesics and are routinely used to good effect both for perioperative analgesia and for the control of cancer pain. However, there is conflicting evidence of how opioids may impact on the cancer itself, with a variety of mechanisms postulated—some potentially useful in disease control, with others being detrimental.

So how might opioids interact to affect tumour growth?

*In vivo* and *in vitro* studies have yielded conflicting results, with opioids either inhibiting or promoting cancer cell growth, with a recent review summarizing the range
of studies that have investigated opioid effects on tumour growth, some of which may be via a direct effect on opioid receptors and others which may involve intracellular modification of other systems, such as the vascular endothelial growth factor receptors. This is complicated further by the fact that type of opioid, route and duration of administration, and dose may all be relevant factors. There is evidence for a biphasic effect of opioids, with chronic high-dose opioids suppressing tumour growth in rodent models, whereas single- or low-dose opioids, typical of perioperative use, may promote tumour growth.25

Changes in opioid receptors have also been studied, in particular, the mu-opioid receptor (MOR). An up-regulation of MOR has been found in some types of non-small cell lung cancer, with in vitro and in vivo rodent studies, showing that overexpression of MOR can result in increased tumour growth and metastases. Interestingly, the use of a peripheral MOR antagonist, methylnaltrexone, seemed to prevent increased tumour growth, as did silencing MOR expression using knockout techniques.34–36

What is the clinical evidence for the involvement of opioids in cancer processes?

The clinical evidence is as yet limited, with many of the studies being retrospective, with variable access to comprehensive data on opioid use. For example, a retrospective study of 655 patients with colorectal cancer found that there was an increased risk of death up to 5 yr later (all-cause mortality) in patients receiving patient-controlled analgesia (morphine) compared with epidural analgesia (local anaesthetic and fentanyl or morphine), only in those patients with rectal cancer, but not colon cancer. Common to the majority of studies investigating the benefits of regional techniques, the anaesthetic technique itself involved the administration of opioids.25

The role of the endogenous opioid system in cancer biology remains poorly understood, although a recent study of >2000 women with breast cancer found that a particular single-nucleotide polymorphism of the MOR gene (A118G) may be associated with an increased likelihood of survival at 10 yr. Thus, in those women with invasive disease, who had the G/G allele, there was a better chance of survival than for those with A/G or A/A. While an important finding that requires further study, the possibility of confounding factors needs to be considered: there is no information about whether the patients were on strong opioids, whether they had pain, and how it was controlled, nor indeed, what oncological treatment they received.37 It is already known that people with at least one of the G alleles have a reduced analgesic response to opioids.38 39

So, there is evidence that regional techniques may be beneficial, and opioids may have effects on cancer biology but much more work needs to be done to clarify what it is about regional techniques that is of potential benefit, and whether indeed opioid analgesia may not always be ideal for cancer patients. In one of the few multicentre randomized controlled trials of intrathecal analgesia in cancer patients, there was a benefit from intrathecal analgesia—this did include opioids as well as local anaesthetics.40 What we may be seeing are the results of good pain control, rather than specific effects of the agents themselves.

Certainly, the European Association for Palliative Care has concerns that adverse reports about morphine in cancer may result in harm to patients, by denying them good pain relief, when in fact the scientific evidence remains unclear (http://eapcnet.wordpress.com/2012/03/30/do-opioids-influence-cancer-growth-the-iahpc-perspective-3/). Intriguingly, patients with widespread chronic pain appear to have a higher mortality from cancer than people who do not have chronic pain.41 This, in combination with the evidence discussed here, leaves us with the question: is the best way to reduce cancer recurrence to provide optimum analgesia throughout the course of the disease, rather than to limit the use of opioids?

Declaration of interest

None declared.

References

11. Deegan CA, Murray D, Doran P, et al. Anaesthetic technique and the cytokine and matrix metalloproteinase response to...
14 Singleton PA, Moss J. Effect of perioperative opioids on cancer recurrence: a hypothesis. Future Oncol 2010; 6: 1237–42
19 Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006; 105: 660–4
34 Lennon FE, Moss J, Singleton PA. The mu-opioid receptor in cancer progression: is there a direct effect? Anesthesiology 2012; 116: 940–5