

Anaesthesia and cancer surgery: Is there an effect on outcome?

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Surgery for cancer can release malignant cells into the circulation, some of which may develop into metastases. The major first-line defence against the development of primary tumours and metastatic spread of established tumours is natural killer (NK) cells. Because general anaesthesia may suppress this immune response [1] there has been considerable interest in a possible association between anaesthesia and the subsequent proliferation and recurrence of cancer [2]. Could our choice of anaesthesia increase the risk of cancer recurrence that could kill the patient, or might a more appropriate choice of agent decrease the risk of recurrence after cancer surgery? In this lecture I will discuss the evidence for and against such an association, in particular looking at the roles of volatile and intravenous anaesthetics, opioids and other analgesics, and the potential advantages of regional anaesthesia.

Inhalational anaesthetics

Because volatile anaesthetics suppress the immune system, including reducing the cytotoxicity of NK cells, they may increase the risk of recurrence in patients undergoing cancer surgery [3,4]. Several recent reviews have raised the possibility that inhalational anaesthesia may be a factor in the recurrence of malignant disease after cancer surgery [3,5]. One recent study, however, has thrown doubt on an association between general anaesthesia and the subsequent development of cancer [6]. In a cohort of 2792 cancer-free patients neither the duration nor the depth of sevoflurane anaesthesia was associated with an increased risk of new malignant

diseases within 5 years of surgery. However, these results do not exclude the possibility that anaesthesia may be potentially detrimental in patients with pre-existing cancer.

IV agents

Total intravenous anaesthesia (TIVA) has been proposed as an alternative to inhalational anaesthesia [5]. Propofol is the most popular hypnotic used in TIVA, and may be the anaesthetic of choice in patients with cancer. It attenuates the adverse immune response to surgery and has anti-tumour activity, possibly related to inhibition of cyclo-oxygenase, thus restricting angiogenesis, a key factor in the growth and dissemination of cancers [7,8]. On the other hand there is evidence that propofol (and midazolam) may have a negative influence on the immune system, by suppressing neutrophil chemotaxis and phagocytosis. Midazolam also suppresses immune cell adhesion and decreases NK cell activity [9]. In contrast to propofol, ketamine significantly reduced NK activity and increased lung tumour retention and lung metastases in rats [10].

Opioids

Opioids, whether used in the peri-operative period or for long term pain management, can influence outcome in patients with cancer. However, the results of studies investigating the actions of opioids on cancer are conflicting, with reports of both inhibition and stimulation of cancer cell growth and metastatic proliferation by opioids [11]. Even

within one cell type, e.g. small cell lung cancer cells, opioid-induced proliferative and anti-proliferative effects have been described [12]. It is likely that the overall effect depends on factors such as type of cancer, presence of pain, the dose and timing of the opioid, and the duration of exposure.

Opioids have a number of properties that enable them to promote the proliferation and spread of malignant cells, including stimulation of angiogenesis [12]. The μ -opioid receptor (MOR) is extensively expressed in non-small cell lung cancer and MOR knock-out mice developed significantly fewer tumours than wild-type mice when injected with lung cancer cells, indicating that the opioid receptor MOR has a significant effect in promoting lung cancer [13]. Both morphine and fentanyl dose-dependently suppress NK cell activity [11,14]. In cancer patients immunosuppression induced by high dose chronic opioid therapy can worsen the course of the disease. A recent retrospective analysis suggests that intra-operative sufentanil is associated with an increased risk of cancer relapse after radical prostatectomy for prostate cancer [15]. In contrast, however, others have reported that chronic high dose administration of opioids is more likely to suppress rather than promote the growth of malignant tumours (whereas single or low doses are more likely to enhance tumour growth [12]). There is no evidence that the use of opioids to treat acute severe pain has a negative effect in patients with cancer. Pain suppresses NK-cell activity and promotes tumour development in animals, making pain management particularly important in the cancer surgery patient [4].

NSAIDS

Increased expression of COX-2 occurs in many types of cancers and NSAIDs, especially those with COX-2 inhibitory activity, can reduce significantly the risk of colon, breast and prostate cancers. There are, therefore, good arguments for using COX-2-specific in-

hibitors in anaesthesia. In addition to providing analgesia thereby reducing the amount of opioid needed for optimum pain relief, they can contribute to minimizing the risk of tumour spread and growth. Also the non-specific COX-inhibitor ketorolac, given IV as a single dose immediately before skin incision, significantly reduced cancer recurrence after surgery for breast cancer [16].

Regional anaesthesia

The main rationale for a possible protective effect of regional blocks on cancer recurrence is that regional analgesia may preserve immune defences against tumour. A number of studies have investigated the influence of regional anaesthesia, most commonly epidural anaesthesia, on outcome after surgery for prostate, breast and colon cancer. These studies have been recently reviewed [17]. Most studies reported a decrease in the incidence of metastases and cancer recurrence in patients who underwent surgery with combined general anaesthesia-epidural analgesia compared with those given general anaesthesia plus opioids. Other studies, however, reported equivocal findings or found no benefit from regional anaesthesia [15-19]. Unfortunately the majority of studies of epidural anaesthesia in cancer patients have been retrospective and have investigated regional combined with general anaesthesia, often with other drugs that could have influenced the outcome, e.g. NSAIDs.

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