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REVIEW ARTICLES

Effect of anaesthetic technique and other perioperative factors on cancer recurrence

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Key points

- Metastatic disease is the most important cause of cancer-related death in patients after cancer surgery.
- Drugs and techniques used perioperatively may influence outcome.
- *In vitro* and animal study evidence suggests potential mechanisms altered by anaesthetic drugs.
- Human studies are limited but regional anaesthesia may be beneficial.
- There is a need for large-scale prospective studies.

Summary. Surgical excision is the mainstay of treatment for potentially curable solid tumours. Metastatic disease is the most important cause of cancer-related death in these patients. The likelihood of tumour metastases depends on the balance between the metastatic potential of the tumour and the anti-metastatic host defences, of which cell-mediated immunity, and natural killer cell function in particular, is a critical component. It is increasingly recognized that anaesthetic technique and other perioperative factors have the potential to effect long-term outcome after cancer surgery. Surgery can inhibit important host defences and promote the development of metastases. Anaesthetic technique and drug choice can interact with the cellular immune system and effect long-term outcome. The potential effect of i.v. anaesthetics, volatile agents, local anaesthetic drugs, opiates, and non-steroidal anti-inflammatory drugs are reviewed here. There is particular interest at present in the effect of regional anaesthesia, which appears to be beneficial. Retrospective analyses have shown an outcome benefit for paravertebral analgesia for breast cancer surgery and epidural analgesia for prostatectomy. Blood transfusion, pain, stress, and hypothermia are other potentially important perioperative factors to consider.

Keywords: anaesthesia; cancer; outcome; perioperative

The potential effect of anaesthesia on long-term patient outcome is increasingly acknowledged.[1] The purpose of this article is to review the literature regarding the potential long-term effect of anaesthetic technique and other perioperative factors in a field of emerging interest and importance—long-term outcome after cancer surgery.

An analogy has been made between developing postoperative wound infection and postoperative metastasis.[2] In both situations, the principle is that the perioperative period is a critical time and that suppression of host defence mechanisms at this time can have deleterious long-term consequences. It has long been recognized that anaesthetists play a role in preventing postoperative wound infection. The role of the anaesthetist in improving long-term outcome after cancer surgery is still emerging. The concept that interventions occurring during the perioperative period will have an effect on long-term outcome after cancer surgery is based on what is known about tumour biology and host defence mechanisms, and so these areas will be reviewed here. This article will also review the known effects of anaesthetic technique and other perioperative factors on host defence mechanisms and discuss their potential consequences. Much of the science is based on

in vitro testing and on studies using animal models. Where possible, this article will focus on results from human studies. Important factors which may affect oncological outcome, such as neoadjuvant chemotherapy, preoperative radiotherapy, and the timing of surgery, which are not under the primary control of the anaesthetist, are beyond the scope of this review.

The literature in this review was obtained from a search of the PUBMED© database up until January 15, 2010. Results were restricted to the English language. Search terms included 'tumour metastases and anaesthesia', 'anaesthesia and natural killer cells', 'i.v. anaesthetic drugs and cancer', 'volatile anaesthetic drugs and anaesthesia', 'opiates and cancer', 'local anaesthetic drugs and cancer', 'regional anaesthesia and cancer', 'epidural anaesthesia and cancer', and 'perioperative blood transfusion and cancer recurrence'. Relevant references from the articles identified in the literature review were also obtained, and all primary sources were retrieved.

Cancer remains a significant cause of morbidity and mortality internationally. In the USA, it is the second most common cause of death, exceeded only by heart disease and accounting for one in every four deaths.[3] There are

more deaths due to cancer than cardiovascular disease in people <85 yr. It is estimated that there were 1.5 million new cancer diagnoses and more than 500 000 deaths in the USA in 2009. The most common cancers contributing to mortality are lung, prostate, breast, and colorectal cancer.[4]

## The pathogenesis of tumour metastases

The likelihood of tumour metastases depends on the balance between the metastatic potential of the tumour and the anti-metastatic host defences.[5] One hypothesis of how a tumour acquires metastatic potential, referred to as 'seed and soil'[6] (Fig. 1), describes a progressive growth of the primary tumour, during which time the nutrient supply is initially met by diffusion, but later requires neovascularization. Angiogenic factors are synthesized and secreted, and a capillary network arises from adjacent host tissue. Tumour cells, which are genotypically and phenotypically diverse, then enter the host circulation, most commonly via the lymphatic system. These tumour cells detach and embolize. Most of these cells will be destroyed by the host immune defences described below.

Tumour cells that survive will become trapped in the capillary beds of distant organs, extravasate, proliferate, and ultimately develop their own blood supply. The mediators of this process of angiogenesis include vascular epidermal growth factor (VEGF) and prostaglandin E2.[7] These cells are now micrometastases and in turn have their own metastatic potential. It is now recognized that metastases will only develop in specific organs and this is a result of biologically unique micro-environments.[8] The tumour cells themselves are the product of an evolutionary process during which they randomly mutate and undergo selection.

Initially, tumour cells are weakly antigenic and do not elicit an immune response. This has been referred to as a phase of unchecked proliferation and random mutation.[5] As they mutate further, they become more antigenic. This is a phase of recognition, elimination, and selection of immune-resistant
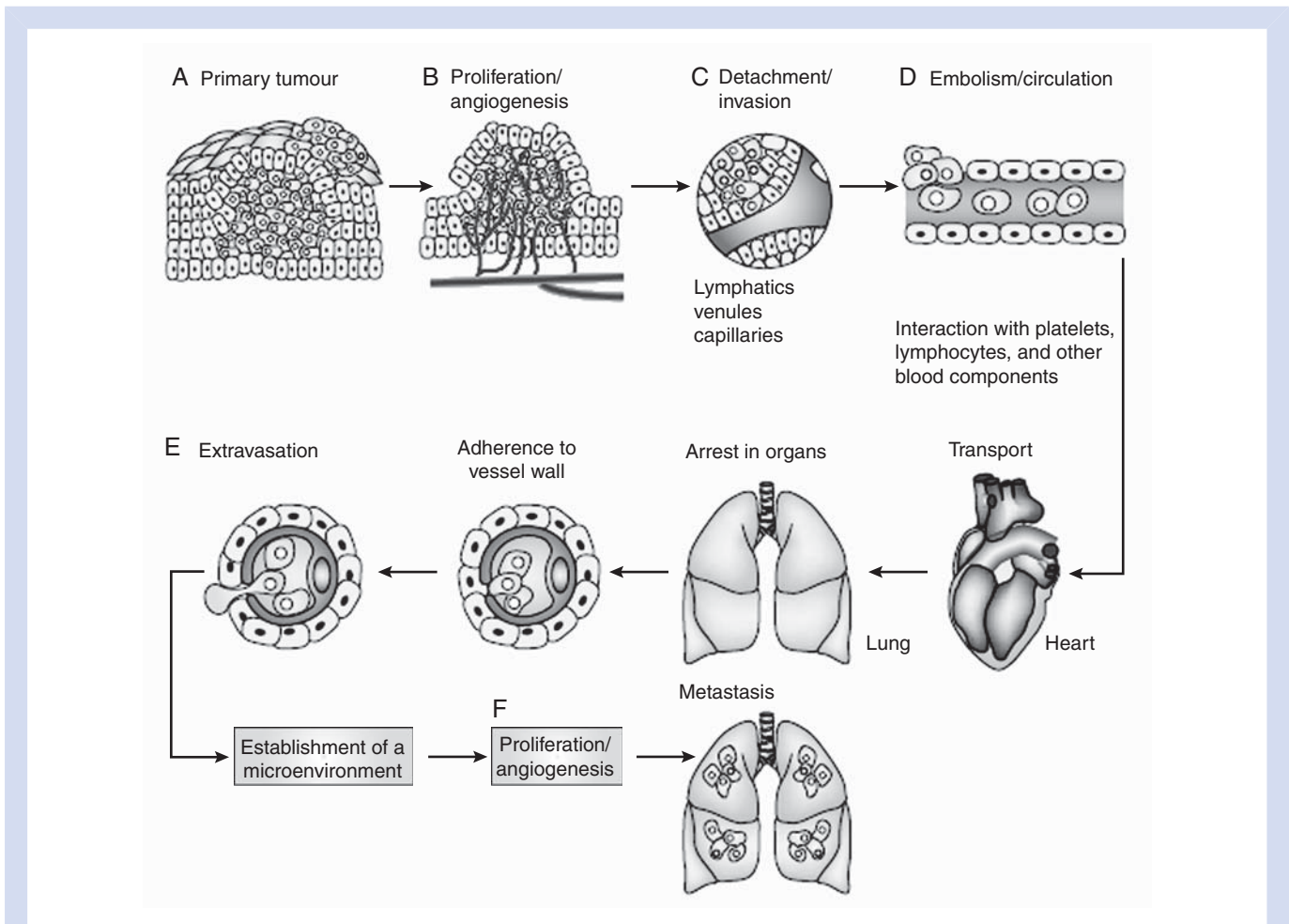
Fig 1 The main steps in formation of a metastasis.[6] (A) Cellular transformation and growth, a period during which nutrient supply is met by diffusion. (B) A phase of extensive cell proliferation and angiogenesis. (C) Tumour cells invade host stroma, detach, and may enter channels such as lymphatics. (D) Embolization of single tumour cell or aggregates occurs. Most circulating tumour cells are rapidly destroyed but some may become trapped in capillary beds by adhering to capillary endothelial cells or to the subendothelial basement membrane. (E) Extravasation. (F) Proliferation within the organ parenchyma completes the metastatic process. Reprinted by permission from Macmillan Publishers Ltd.[6] ©2003.

cells. Ultimately, the tumour cells develop escape mechanisms to evade the host immune response (Fig. 2).

Response of an intact cellular immune system to the presence of tumour cells

An intact cellular immune system is the critical host defence against the development of metastases.[5] Natural killer (NK) cells are the primary defence against cancer cells.[9] They are a subpopulation of large granular lymphocytes that spontaneously recognize and lyse tumour cells. Multiple studies show an inverse relationship between NK cell activity at the time of surgery and the development of metastatic disease. Patients with a low level of NK cell activity have been reported to have a higher incidence of cancer.[10] Animal studies have shown that stress-induced reduction in NK cell activity can cause enhanced tumour development.[11] Interleukin-2 (IL-2) and interferon-γ (IFN-γ) are important activators of NK cells.[12]

Cytotoxic T-cell function has been demonstrated to be another important component. For instance, patients with high cytotoxicity against their primary localized lung cancer have been shown to have complete remission at 5 yr, whereas none of the patients in the same study who had low cytotoxicity survived.[13] Mononuclear cells and dendritic cells also have anti-metastatic functions.

The importance of an intact cellular immune system can be demonstrated in the context of solid-organ transplant recipients.[14] Immunosuppressive therapy in these patients appears to promote the development of metastases. Patients with sarcomas, melanoma, myeloma, skin, bladder, and kidney tumours all have a higher recurrence rate if they are on immunosuppressive therapy.

As mentioned previously, the eventual emergence of tumour cells that can evade host cellular immunity is a key step in the development of metastasis. Tumour cells from metastases in immunocompetent mice show genetic lesions which protect them from host immunity. Those from metastases in immunocompromised cells do not.[15]

Cell-mediated immunity does not eradicate the primary tumour; however, it may eliminate minimal residual disease. Many patients have residual cancer cells in sites such as bone marrow but do not go on to develop overt metastases.[16]
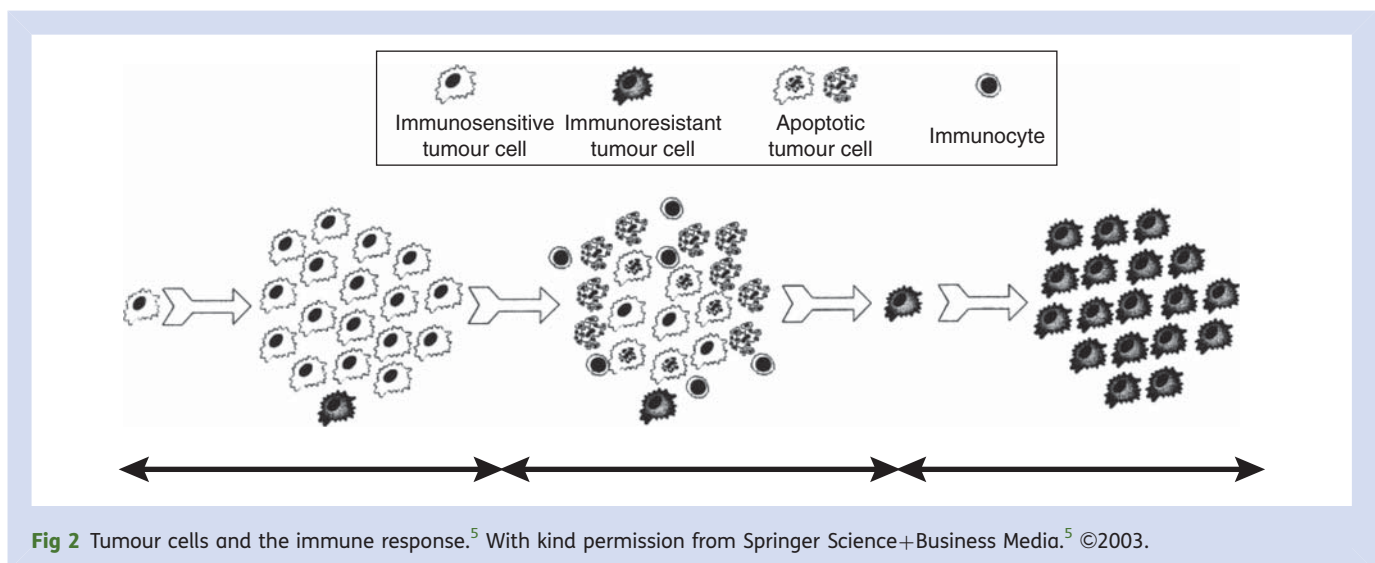
The effect of surgery on host defence mechanisms and metastatic development

Surgical excision is the mainstay treatment for solid tumours. 'Minimal residual disease' is the term used to describe the tumour cells that remain after curative resection. These can be microscopic deposits at the surgical margins or micrometastases.[17]

Studies in humans have demonstrated that surgery itself can promote the development of metastases, for instance, by inhibiting NK cell activity.[11]

Four potential mechanisms that may promote metastasis after surgery have been proposed (Table 1).

(i) Handling and disrupting the tumour during surgery releases tumour cells into the circulation. Polymerase chain reaction can detect tumour cells in patient blood, and their number has been shown to increase after surgery.[18]

(ii) The presence of the primary tumour may itself inhibit angiogenesis, and therefore, tumour removal may eliminate a safeguard against angiogenesis. This may promote survival and growth of minimal residual disease.

(iii) Local and systemic release of growth factors during surgery may promote tumour recurrence both locally and at distant sites. EGF and transforming growth factor-β levels are increased, as is VEGF. In addition, anti-angiogenic factors, such as angiostatin and endostatin, may be reduced by surgery.[9]

Fig 2 Tumour cells and the immune response.[5] With kind permission from Springer Science+Business Media.[5] ©2003.

Table 1 Surgical factors that may promote development of metastases

	Proposed mechanism	Example
Handling and disruption of tumour	Release of tumour cells into the circulation	Number of circulating tumour cells shown to be increased after surgery
Decrease in circulating anti-angiogenic factors	Primary tumour may release these factors; removal of the tumour prevents this	Angiostatin and endostatin (both anti-angiogenic) may be secreted by primary tumour
Increase in local and systemic release of growth factors after surgery	Favour growth of metastases	VEGF, EGF levels are increased after operation
Perioperative immunosuppression due to surgery	Cellular immune system suppressed for days; loss of tumour surveillance protection	Decrease in number of circulating NK cells, cytotoxic T-lymphocytes, dendritic cells, and T-helper cells

Table 2 Anaesthetic drugs and host defences

Drug	Potential effect on anti-tumour host defences
Ketamine	Reduced NK cell activity and number in animal models
Thiopental	Reduced NK cell activity and number in animal models
Propofol	Reduced NK cell number in animal models
Volatile agents	Inhibits interferon stimulation of NK cell cytotoxicity in animal models. Reduces NK cell number in humans; associated with worse outcome when compared with local anaesthesia for melanoma excision
Nitrous oxide	Associated with acceleration in development of lung and liver metastases in animal models. No effect on cancer outcome after surgery for colorectal carcinoma in humans. Inhibits formation of haematopoietic cells that may be important for tumour cells
Local anaesthetic drugs	Lidocaine inhibits EGF receptor and tumour cell proliferation *in vitro*; ropivacaine inhibits growth of cancer cells
Morphine	Inhibits cellular immunity including NK cell activity in animal models. Inhibits NK cell activity in humans
Fentanyl	Inhibits NK cell activity in humans
Tramadol	Stimulates NK cell activity in animal models. Stimulates NK cell activity in humans
COX-2 inhibitors	Display anti-angiogenesis and anti-tumour effects in animal models

(iv) There is perioperative immunosuppression, including the cellular immune system. This is a result of both the neuroendocrine and cytokine stress response to surgery,[19] and the effect of anaesthetic technique and other perioperative factors. This is discussed in more detail below.

Much of the literature on the effect of surgery itself on cancer outcome is old and precedes newer, less invasive (e.g. laparoscopic) surgical techniques and neoadjuvant chemotherapy. Laparoscopy is less immunosuppressive than laparotomy.[20] Laparoscopic resection of colorectal carcinoma has been shown to be associated with a longer disease-free survival and time to recurrence when compared with open resection.[21] Increased surgical stress has been shown to augment cancer metastases in a mouse model.[22]

Suppression of the cellular immune system by surgery

Major surgery suppresses cellular immunity for several days.[5] Humoral immunity remains relatively intact. There is a measurable decrease in the production of cytokines that favour cellular-mediated immunity such as IL-2, IL-12, and IFN-γ, and an increase in the production of cytokines that interfere with cell-mediated immunity, such as IL-10. There is a decrease in the number of circulating NK cells, cytotoxic T lymphocytes, dendritic cells, and T-helper cells.[19] A peak in immunosuppression is said to occur at day 3,[17] and this may be a window of opportunity during which minimal residual disease can grow and spread. Cell-mediated immunity can reduce the likelihood of metastasis even if it had not prevented the primary tumour.[23]

Effect of anaesthetic agents and opioids

The potential effects of drugs used in anaesthesia on host defences have been studied using *in vitro* and animal models, and in some human studies (Table 2).

Intravenous anaesthetic agents

The effect of i.v. anaesthetic agents has been studied in rats that were injected with tumour cells and subjected to anaesthesia with various agents.[24] Ketamine and thiopental both increased the number of viable tumour cells found in the lungs at autopsy, by 5.5- and two-fold, respectively. Lung tumour retention was not increased in rats exposed to propofol and diazepam. In the same study, ketamine and thiopental, but again not propofol, significantly suppressed NK cell activity. All three caused a significant reduction in NK cell number compared with baseline. There was a correlation between the number of viable tumour cells found at autopsy and NK cell activity when all groups were combined, but not when they were analysed separately. The inhibitory effects of ketamine on NK cell activity has been shown in another study.[25]

Interestingly, propofol conjugates (propofol-docosahex-aenoate and propofol-eicosapentaenoate) have been looked at as treatments for breast cancer, as they have been shown to inhibit cellular adhesion, migration, and apoptosis in breast cancer cells.[26]

Inhalation agents

Isoflurane and halothane inhibit IFN stimulation of NK cell cytotoxicity in mice.[27] Multiple studies have demonstrated *in vitro* effects that may have some relevance in the cancer setting. For instance, sevoflurane alters the release of cytokines (IL-1β and TNF-α, but not IL-2) by NK and NK-like cells *in vitro*.[28]

Human data are more difficult to interpret because of confounding variables and the multiple drugs to which patients are exposed to. One large retrospective analysis found that general anaesthesia for excision of primary melanoma was associated with a decrease in the survival rate (relative risk of 1.46) compared with local anaesthesia.[29] The difference was attributed to the use of general anaesthetic agents. General anaesthesia decreases circulating NK cells in patients undergoing elective orthopaedic surgery.[30] Neutrophil, macrophage, dendritic, and T-cell function are also impaired.[31]

Nitrous oxide

Nitrous oxide interferes with DNA, purine, and thymidylate synthesis and depresses neutrophil chemotaxis.[32] This inhibits formation of haematopoietic cells that may be relevant in tumour surveillance. Neutrophil function is depressed, and mononuclear cell production is reduced. In a mouse model, nitrous oxide exposure has been shown to be associated with acceleration in the development of lung and liver metastasis, and it was the most potent stimulator of liver metastasis of the anaesthetic drugs studied.[33]

The effect of nitrous oxide exposure on cancer recurrence in humans after surgery for colorectal carcinoma has been examined by re-analysing a subpopulation of an earlier study designed to look at the effect of nitrous oxide on wound infection after colectomy.[34][35] One group had been exposed to 65% nitrous oxide and oxygen, whereas the other group received 65% nitrogen and oxygen. There was no difference detected between the two groups in terms of cancer recurrence. Follow-up was at 4–8 yr.

Local anaesthetic drugs

An anti-tumour effect of lidocaine has been observed *in vitro* using a human tongue cancer cell model.[36] Lidocaine, at clinical concentrations, was shown to have a direct inhibitory effect on the EGF receptor, thereby inhibiting tumour cell proliferation. It has also been shown to inhibit the invasive ability of human cancer cells.[37] Ropivacaine suppresses the *in vitro* growth of cancer cells in patients with ulcerative colitis.[38] There are other reports of local anaesthetics showing anti-proliferative or cytotoxic effects on tumour cells.

Opioids

Opioid administration, both perioperative and chronic, has been shown to suppress cell-mediated and humoral immunity.[31] This includes NK cell activity, production of immune-stimulating cytokines, phagocytic activity, and antibody production.[39]

Morphine suppresses rat NK cell cytotoxicity in a dose-dependent manner.[40] The suppression is naloxone-sensitive. Morphine at clinically relevant doses increases angiogenesis and promotes breast tumour growth in mice.[41] This effect has been shown to be preventable by co-administration of celecoxib.[42]

Opioids also suppress postoperative NK cell cytotoxicity in humans.[43] One group in this study received high-dose fentanyl (75–100 μg kg^{-1}) and the second group received lower dose fentanyl (up to 6 μg kg^{-1}). At 24 h after operation, both groups had similar suppression of NK cell cytotoxicity (~20%). This suppression was more prolonged in the high-dose fentanyl group in which it lasted beyond the second postoperative day. The same study looked at the *in vitro* effect of human recombinant IL-2, IFN-α, and IFN-β. The NK cell suppression seen in this study was fully reversed by IL-2 and partially reversed by IFN-α and IFN-β. This may be a potential target for immunotherapy. This opioid effect may be mediated by the neuroendocrine response they elicit. Healthy volunteers have also been shown to have components of their cell-mediated immunity, including NK cell cytotoxicity, suppressed by a morphine infusion.[44]

In contrast to the above results, a beneficial effect for perioperative, especially preoperative, administration of morphine in rats undergoing laparotomy has been demonstrated.[45] In this study, a surgery-induced increase in tumour retention was attenuated in all rats who received morphine, and this was more marked if the morphine was given before operation. This may suggest a role for preoperative morphine administration as a way to reduce the surgery-induced increase in metastases. Morphine has also been shown to suppress tumour growth and metastasis in a rat model that looked at the effect of relieving cancer pain in rats inoculated with melanoma cells.[46]

Tramadol, which has noradrenergic and serotonergic activity in addition to its action at opioid receptors, stimulates NK cell activity, both in rodents and humans.[47] Also in a rat model, tramadol has been shown to block the enhancement of lung metastasis induced by surgery and also to prevent the surgery-induced suppression of NK cell activity.[47] Morphine does not show these effects.

The differences between morphine and tramadol have been shown in humans undergoing hysterectomy for uterine carcinoma, who were given either morphine 10 mg or tramadol 100 mg immediately after surgery.[48] T-lymphocyte proliferation was depressed in both the tramadol and morphine groups, but remained depressed only in the morphine group. Neither surgery nor morphine affected NK cell activity, whereas tramadol was shown to enhance NK cell activity. Long-term outcome was not reported.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis via inhibition of the cyclooxygenase (COX) enzyme. Tumour cells have been shown to secrete prostaglandins,[49] and this may be a mechanism to evade host cell-mediated immunity. COX-2 inhibitors have anti-tumour and anti-angiogenic properties in a rat model.[50] This has been recently demonstrated in the perioperative setting, again using a rat model.[51] A COX-2 inhibitor (etodolac) was shown to attenuate the deleterious effect of surgery on lung tumour retention. When combined with propranolol, it abolished it. A single preoperative dose was effective. Celocoxib, a COX-2 inhibitor used clinically, has been shown to inhibit chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis, and mortality in mice.[42]

Breast cancer cells over-express COX-2. Women on long-term COX-2 inhibitors may have a lower incidence of breast cancer.[52] A phase III trial of an aromatase inhibitor combined with celocoxib in women with advanced breast cancer did not result in any significant advantage compared with the aromatase inhibitor alone.[53]

Other perioperative factors

Effect of regional anaesthesia

There have been two major retrospective analyses on this topic (Table 3). One showed a 57% reduction in incidence of biochemical cancer recurrence when epidural analgesia was used for open prostatectomy when compared with post-operative opioid analgesia (follow-up interval of 2.8–12.8 yr).[9] The other showed a four-fold reduction in the incidence of recurrence or metastasis in patients who received general and paravertebral anaesthesia and analgesia when compared with general anaesthesia and morphine analgesia for primary breast cancer surgery (median duration of follow-up of 32 months).[2] More recently, there has been a secondary analysis of patients randomized to general anaesthesia with or without epidural for radical prostatectomy.[54] The primary endpoints of the trial were analgesia, blood loss, and need for blood transfusion. Secondary analysis did not show a difference between the two groups when analysed for clinical or biochemical recurrence of prostate cancer.

To date, there are no published prospective human trials designed specifically to look at the effect of regional anaesthesia on cancer outcome. The Outcomes Research Consortium (Cleveland Clinic, USA) has initiated multicentre randomized controlled trials looking at paravertebral anaesthesia and analgesia for breast cancer surgery (NCT00418457)[55] and epidural anaesthesia and analgesia for laparoscopic colorectal cancer surgery (NCT00684229). The primary endpoint for these trials is cancer recurrence.

A number of studies using animal models demonstrate the biological plausibility of an effect of regional anaesthesia on long-term outcome after cancer surgery. A key study using a rat model demonstrated that sevoflurane general anaesthesia and laparotomy each suppress tumoricidal function in liver mononuclear cells (T-helper cells) and that

Table 3 Retrospective analyses suggesting benefit for regional analgesia

	Exadaktylos and colleagues[2]	Biki and colleagues[9]
Study design	Retrospective	Retrospective
Surgery	Mastectomy and axillary clearance for breast cancer	Open radical prostatectomy for prostate cancer
Total number of patients	129	225
Regional technique used	Paravertebral catheter placed at T2 or T3 level; used intra-operatively and for 48 h after operation	Thoracic epidural placed at T11; used for 48–72 h after operation
Control group	Balanced general anaesthesia with postoperative patient-controlled morphine analgesia	Balanced general anaesthesia with postoperative patient-controlled morphine analgesia
Duration of follow-up	32 (5) months	2.8–12.8 yr
Endpoint	Recurrence- and metastasis-free survival	Increase in prostate-specific antigen levels
Result	94% in paravertebral group vs 77% in control group at 36 months	Kaplan–Meier recurrence-free survival estimate at final observation was 76% in epidural group vs 49% in control group

spinal block attenuates this effect.[56] This study also showed fewer liver metastases in the sevoflurane plus spinal anaesthesia group compared with the sevoflurane without spinal group.

The beneficial effect of spinal anaesthesia on lung tumour retention in rats undergoing laparotomy has been shown in another study.[57] One group received halothane general anaesthesia and systemic morphine, whereas the other group received halothane general anaesthesia, but with the addition of spinal bupivacaine and spinal morphine. The control groups were either anaesthetized or left undisturbed, whereas the other groups had a laparotomy. The laparotomy plus general anaesthesia group had a 17-fold increase in lung metastasis. Spinal block reduced this by 70%. There was also a reduction in the cytotoxic activity of NK cells in the presence of surgery and general anaesthesia compared with the control group. The conclusion here was that surgical stress in rats promotes the development of metastasis and that this effect is markedly attenuated by regional anaesthesia.

The effect of regional anaesthesia on human breast cancer cells *in vitro* has also been examined.[58] Serum from patients who received propofol/paravertebral anaesthesia was found to inhibit proliferation but not migration of an

oestrogen receptor-negative breast cancer cell line when compared with a sevoflurane/opioid group. This was felt to be important because of a correlation between increased cellular proliferation rate and worse prognosis in untreated patients.[59]

The potential ability of regional anaesthesia to improve long-term outcome after cancer surgery can be attributed to at least three different mechanisms.[31] First, regional anaesthesia attenuates the immunosuppressive effect of surgery. Neuraxial anaesthesia can inhibit the neuroendocrine stress response and paravertebral analgesia in humans having breast surgery has also been shown to inhibit this surgical stress response.[7] Secondly, patients who receive regional analgesia have lower opioid requirements. Paravertebral analgesia can reduce opioid requirements after breast surgery.[60] Opioids may themselves inhibit cell-mediated immunity and host anti-tumour defences. Finally, when regional anaesthesia is used in addition to general anaesthesia, the amount of general anaesthetic required during surgery is reduced.

Effect of acute pain

Acute pain suppresses NK cell activity.[61] [62] Optimizing postoperative pain management may attenuate the post-surgical inhibition of host anti-tumour defence mechanisms, including of NK cells. This has been demonstrated in a rat model.[63]

The potentially deleterious effects of acute pain are difficult to separate from the effects of opioids discussed above. One conclusion is that opioids improve *in vivo* cancer resistance only in the setting of postoperative pain and that opiates given under basal conditions can be immunosuppressive and pro-metastatic.[64]

Effect of blood transfusion

Perioperative allogeneic blood transfusion may be associated with an increased risk of tumour recurrence.[65] The immunosuppressive effect of allogeneic blood, referred to as transfusion-associated immunomodulation (TRIM), is a commonly cited explanation.[66] Laboratory evidence of immune suppression includes a reduction in T-helper cell and NK cell count, and a reduction in cytokine production including IL-2 and IFN-γ.[67–69] A similar reduction in immune function has been demonstrated in patients who required a transfusion during surgery for colorectal cancer.[70]

Although the precise mechanism of TRIM is not fully understood, animal studies have demonstrated that the transfusion of allogeneic white blood cells is an important component.[69] A study investigating patients undergoing resection of gastric cancer randomized patients to allogeneic or autologous transfusion.[71] IFN-γ, T-helper cell, and T-helper/cytotoxic T-cell ratio were reduced in both groups after operation. The reduction was greater in the allogeneic transfusion group. Five days after the operation, levels had returned to baseline for patients receiving autologous tranfusions but remained suppressed in the allogeneic group.

Observational studies designed to examine the effect of TRIM on cancer recurrence have shown conflicting results. Severity or stage of the cancer, and co-morbid conditions, are confounding factors that influence the requirement for transfusion.[72] A recently reported observational trial documented outcomes of patients requiring red cell transfusions during thoracic resection of oesophageal cancer.[73] The requirement for blood transfusion was significantly associated with inferior survival. Mandatory leucocyte depletion of blood did not affect survival. None of three randomized trials of patients undergoing resection of a colorectal tumour[74–76] showed an improved cancer outcome with reduction of allogeneic white blood cells. The questions of whether TRIM is associated with a worse oncologic outcome, and of whether leucodepletion reduces TRIM, remains unanswered.

Immunotherapy

Pre-treating rats with an IFN inducer increases NK cell activity to above baseline in rats and attenuates the fentanyl-induced suppression to above baseline levels.[40] There is also some evidence in rats that administration of IFN-α and IFN-β before surgery may offset some of the inhibition of NK cell cytotoxicity associated with surgery and anaesthesia.[77] Immunotherapy for cancer in humans has had only modest success; however, it has been proposed that using it during the critical perioperative period may produce better results.[78]

Hypothermia and anxiety

Hypothermia to 30°C in rats has been shown to suppress NK cell activity and also suppress resistance to metastasis using a specific tumour model.[79] Hypothermia to 33–35°C was not shown to have the same effect.[24] In humans, mild hypothermia to 35.5°C exacerbates the immunosuppressive effects of abdominal surgery.[80] Exposure to cold stimulates a glucocorticoid and sympathetic response, and this may mediate these effects.

Social confrontation and swim stress suppress NK cell activity in rats and increase lung tumour retention.[81] Psychological stress, such as that related to surgery, has been shown to contribute to perioperative immunosuppression in humans.[12] Stress level in cancer patients is associated with the degree of postoperative immunosuppression. It has been shown to predict NK cell toxicity and T-cell responses. This is another area of emerging interest that may have relevance for anaesthetists who deal with patients in the perioperative period.

Discussion

The importance of cellular immunity in long-term outcome after cancer surgery has been well demonstrated. Animal models and human studies both point to NK cell activity in the perioperative period as being a critical factor in determining outcome after potentially curative surgery. Other components of host immunity play important roles. The possible interaction between factors under the control of

the anaesthetist, such as anaesthetic technique, and cellular immunity is becoming increasingly clear. For instance, there are multiple reports of specific drugs effecting NK cell activity.

The next step must be studies that look not only at the effect of anaesthetic technique and other perioperative factors on markers such as NK cell activity, but also at their effects on long-term cancer outcome. Retrospective analyses have already shown a potential benefit on cancer outcome with regional techniques for breast and prostate cancer surgery, and prospective randomized controlled trials in this area are underway. Other areas for future research would include the possible effect that different opiates may have on cancer outcome. As mentioned previously, tramadol may have unique benefits. COX-2 inhibitors also warrant further investigation, as a single preoperative dose has demonstrated anti-tumour effects in mice. The other factors discussed above, such as perioperative anxiety and postoperative pain, are also areas for future research. Interventions here may improve patient quality of life and survival.

In the meantime, this is a rapidly evolving and exciting area, but not one that is completely new. More than 30 yr ago, it was observed that patients who received ether anaesthesia had worse survival rates than patients who received halothane anaesthesia for their primary breast cancer surgery.[82] This was attributed to the effect of the anaesthetic on the 'pituitary–adrenal system' and the 'role of immunity in tumour cell implantation and growth of metastases'.

Conflict of interest

None declared.

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