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ORIGINAL RESEARCH ARTICLE

Regional anaesthesia and analgesia for cancer surgery

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Abstract

The evolution of cancer cells in clinical metastases depends on anti-metastatic immune activity and the ability of the tumour to proliferate and generate new blood vessels (neoangiogenesis). Surgery by itself can depress cellular immunity and functions of cytotoxic T lymphocytes and natural killer (NK) cells. The perioperative stress response releases tumour cells into the circulation and anaesthesia further reduces immune functions, including the functions of neutrophils, macrophages, dendritic cells, T lymphocytes and NK cells. Effective treatment of postoperative pain could play an important role in limiting the metastatic migration following oncology surgery. Opioids used intraoperatively and postoperatively inhibit cellular and humoral immune functions in humans and have natural pro-angiogenic properties. In a retrospective analysis, paravertebral anaesthesia and analgesia for breast cancer surgery reduced the risk of recurrence or metastasis by four during the first years of follow-up. Similarly, following epidural anaesthesia for resection of the prostate, biochemical recurrence of prostate cancer was reduced by 65% and, following colon surgery, the oncological prognosis was enhanced in the first two years. To date there are only retrospective clinical studies available. A prospective, randomized, large-size study focused on cancers with high risk of recurrence is needed to determine if regional anaesthesia and analgesia could have potential for clinically reducing cancer recurrence after oncology surgery.

Introduction

The cellular and immune system has been developed to protect us not only against infectious diseases but also to a distortion of the metabolism of cells division, especially those evolving towards cancer. Reaction to perioperative stress affects our immune system. For most cancers, treatment often involves surgical resection of the primary tumour. Tumour resection surgeries are usually associated with a systemic release of tumour cells. Consequently, we might argue that these patients undergoing oncological surgeries weaken their defence mechanism against metastasis at a critical moment. During oncology surgery, micro-metastasis and spread of tumoral cells (t cells) occur during the procedure.[1–3] The evolution of t cells into clinical metastasis depends mainly on two factors: on one hand, the natural immune antimetastatic activity and, on the other hand, the ability of the tumour to proliferate and to produce new blood vessels (neoangiogenesis).[4–6] This raises the issue of whether or not certain techniques of anaesthesia/analgesia might improve the body's ability to eliminate cancer cells and improve survival, as recent data suggest.

The pathogenesis of tumour metastasis

Tumour metastasis is closely related to the balance between the metastatic potential of the primary tumour and the antimetastatic defence system. A brief description would summarize the different steps of the metastatic genesis as follows:[7] initially, the genotypic and phenotypic ability of some cells from an organ of a host to replicate would be quickly followed by the proliferation of these cells. Local angiogenesis will result as a response to this increase and the nutritional needs of the latter. This neovascularization is typically stimulated by the secretion of proangiogenic factors. Finally,

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neoplasic cells will begin to migrate systemically, particularly through the lymphatics. These cells are initially destroyed by the defence mechanism of the host's immune system. Certain cells will eventually develop immune resistance, associated with multiple metabolic changes, including in their own energy metabolism. Thus, they will be able to migrate within solid organs remote from the primary tumour, where they proliferate, developing their own angiogenesis [notably vascular endothelial growth factor (VEGF) and prostaglandins E2].

The immune system response to the presence of t cells inside the circulatory system depends on the natural killer (NK) cells, lymphocytes which spontaneously recognize and lyse the t cells.[8] Experimental and clinical studies have shown an inverse relationship between NK cells at the time of surgery and the development of distant metastasis. For instance, it is usual to mention that interleukin (IL)-2 and interferon (IFN)-γ are stimulating factors of NK-cell activity, whereas noradrenaline has a rather inhibitory activity. Moreover, this immune defence mechanism also involves cytotoxic T lymphocytes, mononuclear cells and dendritic cells. The integrity of the immune system is essential for host defence against the spread of cancer cells. The increased incidence of metastasis of some cancers (sarcoma, melanoma, bladder and kidney) among patients who receive immunotherapy after transplant illustrates this.

What perioperative factors are involved in the alteration of immune system?

Perioperative factors tip the balance towards an increase in residual disease.

Surgery and surgical stress

The goal of surgery in cancer pathology is ideally to provide a complete resection of the primary tumour cells, allowing the patient's recovery. In practice, the situation appears much more complex. Indeed, some experimental and preliminary clinical studies suggest that surgery could help to promote the development of pre-existing micrometastases and facilitate the appearance of new metastases. Manipulation and excision will be responsible for numerous vascular breaks, promoting the migration of residual tumour cells into the systemic circulation. The surgery will be accompanied by release of cellular growth factors both locally at the the operating site and systemically, and systemic circulation promoting the development of micrometastases. The control of this immune response during the migration of tumour cells and micrometastasis is mainly dependent on cell-mediated immunity: cytotoxic T lymphocytes, NK cells, dendritic cells and macrophages. A number of inflammatory mediators, such as IFN and IL, and in particular IFN-γ and IL-12, and T_h1 cytokines increase the cytotoxic activity of T cells and NK cells. In addition, T_h2-type cytokines are involved in increasing humoral immunity. The suppression of T_h2-type responses greatly impairs the immune response to the oncologic aggression. The surgery releases tumour cells therefore in circulation and depresses cellular immunity, including the functions of cytotoxic T lymphocytes and NK cells.[9–12] Meanwhile, β-adrenergic stimulation, which increases during stress, suppresses NK activity and promotes metastasis. Human studies show that low levels of perioperative NK activity are associated with increased morbidity in cancer.[8] The surgical trauma reduces circulating concentrations of anti-angiogenic factors related to the tumour (angiotensin and endostatin).[13–16] Angiogenesis is a complex process involving components of the extracellular matrix and regulated by multiple angiogenic factors, including IL-6, -8, and -1β; cyclo-oxygenase 2; nitric oxide; tumour necrosis factor and endothelial growth factor.[17,18] Surgery increases the concentrations of pro-angiogenic factors, and releases growth factors that promote local and remote cancer tissue.[5] It is conceptually conceivable, but unproven, that minimally invasive approaches may have less effect on the immune system.

Anaesthesia and postoperative pain

Anaesthesia decreases immune functions, including the functions of neutrophils, macrophages, dendritic cells, T lymphocytes and NK cells.[19–22] Melamed *et al.*[23] demonstrated, in rats, that ketamine, thiopental and halothane reduce the activity of NK cells and generate an increased retention of lung tumours or lung metastases. The number of circulating NK cells per ml of blood was significantly reduced by ketamine and thiopental. The effect of ketamine, in particular, may result from its adrenergic stimulant properties, which suppress the activity of NK cells and promote metastasis. However, propofol does not appear to affect migration or retention of metastases, which may be related to its (low) β-adrenergic-antagonist activity.[24] The treatment of postoperative pain could play an important role in limiting metastatic migration after oncologic surgery. Page *et al.*[11] demonstrated, in rats, that pain relief probably caused

a reduction in stress response and thereby reduced the spread of the metastasis induced by the surgery. They showed also that intrathecal bupivacaine combined with preoperative morphine significantly improved host resistance to a surgery-induced increase of lung metastases.

Opioids

Opiates used during and after surgery inhibit cellular and humoral immune functions in humans.[19,25,26] Moreover, morphine has pro-angiogenic properties and promotes natural breast tumour growth in rats.[27] Opioids also decrease NK cell cytotoxicity (20%), the effect being more prolonged than the dose.[25] However, this aggravating effect is not systematically found and depends on the type of study and model.[28–30] In a mouse model, repeated administration of morphine was associated with a decreased volume of destruction of the original tissue, induced by a decrease in the proliferation of neoplastic cells.[30] For sufentanil and fentanyl, a depression of NK-cell activity is generally reported.[8] However, tramadol would present a very different profile of opioid, characterized by the preservation of NK cell activity.

What is the role of regional anaesthesia/analgesia?

Regional anaesthesia and analgesia should reduce or limit these side effects. Regional anaesthesia attenuates the neuroendocrine stress response related to surgery by blocking afferent neuronal transmission and preventing it from reaching the central nervous system, where it activates the stress response, and by blocking the activation of the descending efferent sympathetic nervous system.[31,32] Perioperative regional analgesia reduces or eliminates the need for agents such as volatile anesthetics or analgesia by opioids.

Data from cell studies

These local anesthetics may act at different levels. Locally, lidocaine inhibits proliferation of human tumour cells of lingual origin by inhibiting the activity of a receptor for epidermal growth factor.[33] Ropivacaine-induced inhibition of cell proliferation of human colonic adenocarcinoma proteins associated with a depolarization of the cell membrane.[34] Similarly, levobupivacaine, bupivacaine and ropivacaine decreased the cell viability of human cancer cells, and have a different effect depending on the cell lines tested.[35] These local effects reported by these earlier studies would suggest the use of a local application of local anesthetics during surgery for cancer. These processes are probably not directly involved in the clinical studies cited earlier in this manuscript, because the doses used are compatible with local doses (0.5–1 mM) and are not systemic. However, this hypothesis of local application remains to be confirmed for different types of cancers and clinical settings.

Data from animal studies

The use of epidural anaesthesia attenuates the response to surgical stress, and prevents the inhibition of the immune system.

As might be expected, it was shown that spinal anaesthesia helps to preserve NK-cell function and reduces the metastatic load to the lungs.[7] Similarly, non-opioid analgesia during and after surgery helps maintain the function of NK cells and reduces the metastatic spread of cancer in rodents.[9–11] More paradoxically, when administered intrathecally, opioids do not seem to exert the same immunosuppressive effects as those observed after systemic administration. This finding has important clinical implications, because the perimedullary analgesia by local anesthetics are often supplemented by small doses of opiates.

Epidural analgesia inhibits the neuroendocrine response and reduces the production of adrenaline and noradrenaline. In a mouse-model study undergoing laparotomy during anaesthesia with sevoflurane, the number of liver metastases increases significantly compared with sevoflurane anaesthesia combined with spinal anaesthesia. Intrathecal local anesthetics attenuated the suppression of tumouricidal function of liver mononuclear cells, probably by preserving the T_h1/T_h2 balance and thereby reducing the production of metastases.[36]

Data from clinical studies

Recent studies seem to emphasize the importance of the association of regional anaesthesia for reducing the incidence of recurrence of secondary solid tumours.[37,38] An initial study was performed in 4329 patients undergoing surgical excision of melanoma under local anaesthesia or general anaesthesia.[39] In this retrospective study, patients undergoing general anaesthesia had a slightly significant higher risk of death during the observation period. A retrospective study by Exadaktylos *et al.*[40] observed 129 patients

with breast cancer undergoing mastectomy with or without axillary dissection under general anaesthesia. Patients were divided into two groups: one group of patients receiving paravertebral block (level T2–T3) with placement of a catheter (initial bolus of 0.2 ml/kg levobupivacaine 0.25% followed by a continuous infusion for 48 hours) and a second group of patients who received analgesia with morphine in patient-controlled analgesia (PCA). During the postoperative period (the first 24 hours), pain scores were significantly lower in the paravertebral group. After 36 months of follow-up, the proportion of patients showing no recurrence of the tumour was 94% in the paravertebral group and 77% in the morphine group (*z*-test $P = 0.007$). The secondary location was most often local or at the level of the axilla (one patient in the regional analgesia group vs 11 in the morphine group), but was also observed at the systemic level (two patients in the regional analgesia group vs eight in the morphine group). A third study, published by Biki *et al.*,[41] was performed retrospectively in patients diagnosed with prostate cancer who underwent prostatectomy by laparotomy under general anaesthesia. The 225 patients were divided into two groups: one group of patients received a thoracic epidural (T11–T12 level) with an initial bolus followed by continuous infusion catheter for 48–72 hours, the second group receiving a intravenous morphine PCA. Perioperatively, few differences are described between the two groups, with no information on pain scores. At the end of follow-up (beyond 9 years), PSA (the primary endpoint of the study) was not significantly elevated in 76% and 49% of cases in men with and without regional analgesia, respectively. These results were not found by the team of Tsui *et al.*[42] whose outcome was identical, but the limitations were numerous: the methodology is not prospective or randomized, and the results are not blindly analysed.[43] In gastrointestinal surgery, the combination of regional anaesthesia and general anaesthesia remains unclear: it could allow an improvement in survival or decrease recurrence with no metastasis at the time of surgery,[44–46] results not found by Myles *et al.*[47] The variety of cancer types included in these studies probably makes it difficult to interpret data. Somewhat controversial results have also be found in gynecological (ovarian) cancer surgery[48–49] and ear, nose and throat (ENT)[50] as part of preliminary results.[51] Major trials are summarized in Tables 1 and 2.

These tables summarize the data and highlights the different courses depending on the study: sometimes very old periods of inclusion, a total disharmony and judging criteria very different from biological parameters for survival.

Prospective randomized trials are needed to confirm these initial results. Among the tests recorded at www.clinicaltrial.gov, two multicentre, prospective randomized trials have emerged: one in breast cancer surgery (for paravertebral block versus thoracic epidural analgesia with morphine; NCT00418457) and the second in colorectal cancer surgery (epidural analgesia or paravertebral block with bupivacaine versus postoperative morphine; NCT 00684229). These studies and their prospects will probably help put regional anaesthesia and analgesia at the focal point of interest in the coming years.[52]

Conclusion

It is too early to recommend specific types of drugs suitable for anaesthesia for cancer surgery or to recommend a technique of regional anaesthesia. If the reduction of halogenated anesthetics or opiates is a major factor, then it might be possible to obtain similar benefits by using drugs such as dexmedetomidine or intravenous lidocaine.[53] Prospective, randomized, large-sized studies, focused on cancers at high risk of recurrence, are needed to determine if regional anaesthesia and analgesia could have potential for a clinically important reduction in cancer recurrence after surgery for cancer. The most demonstrative studies will be undoubtedly those focused on cancers with a high risk of recurrence.

As anaesthestic drugs are given at a point of potentially high vulnerability in terms of dissemination and establishment of metastasis, there is an urgent need to determine the most appropriate anaesthestic strategy for surgical oncology so that optimal techniques are used to maximise long term survival.

TABLE 1 Regional anaesthesia and cancer surgeries

Reference	Surgery	Anaesthesia technique	Patients	Survival	Criteria
Gupta A. *et al.*[46] Retrospective analysis Inclusion period 2004–2008	**Inclusion criteria** Colorectal surgery stage 1–3 **Exclusion criteria** Cancer stage 4, coelioscopy, non elective surgery	655/750 patients 562 patients: GA + epidural (LA ± fentanyl) vs 92 patients: GA + PCA morphine Duration 2–5 days	**Mean age in years [range]** Colon: 73.3 [21–96] Rectum: 68.6 [25–92] **ASA 3–4:** Colon: 68/360 Rectum: 37/295	**% years**: Dead Colon 72/360 Rectum 77/295	**Mortality:** Multifactor analysis **Colon**: Age > 72 years, Cancer stage 3 vs 1 **Rectum** Age > 72 years, PCA vs epidural Cancer stage 2–3 vs 1 **Kaplan–Meier (5 years):** Rectum Death PCA > epidural ($P = 0.02$)
Myles *et al.*[47] Retrospective analysis based on a prospective randomized trial Inclusion period 1995–2001	**Inclusion criteria** Cancer abdominal surgeries **Exclusion criteria** Non-cancer abdominal surgeries Incomplete surgeries	446/506 patients/ candidates 230 patients: GA + thoracic epidural T4 216 patients: GA + PCA morphine Duration 72 hours	**Age in years** Epidural: 71 PCA: 70 **TNM score** *T3–T4* Epidural: 73/230 PCA: 60/216 *N1–N2* Epidural: 45/230 PCA: 38/216	Recurrence rate or death at 15 years and 5 years Epidural vs GA, ns $P > 0.05$ **Predictive factors:** Age, female sex, transfusion	Recurrences or death Epidural 2.6 years (IQR: 0.7–8.7) PCA Morphine 2.8 years (IQR: 0.7–8.7)
Christopherson *et al.*[44] Retrospective analysis based on a prospective randomized trial Inclusion period 1992–1994	**Inclusion criteria:** Cancer abdominal surgery **Exclusion criteria**: MI < 6 months Abdominal surgery < 3 months Previous chemotherapy or immunotherapy	177/247 patient candidates 92 patients: GA + epidural bupivacaine, analgesia T6+ 85 patients: GA + PCA morphine	**Age in years** Epidural: 68.6 (77) PCA:69.1 (7.8) **ASA III–IV** Not measured **Stage III–IV** Epidural: 24/92 GA: 41/85		Survival with or without prior metastasis **Kaplan–Meier (120 months), survival** *Without prior metastasis* Epidural > GA only between 2.5 and 4 years; survival benefit 1.5–2 years *With prior metastasis* GA > epidural after 1 year

GA, general anaesthesia; IQR, interquartile range; MI, myocardial infarction; ns, not significant; PCA, patient-controlled analgesia; TNM, the TNM staging system is based on the extent of the tumour (T), whether cancer cells spread to nearby (regional) lymph nodes (N), and whether distant (to other parts of the body) metastasis (M) has occurred.

TABLE 2 Regional anaesthesia and non-abdominal surgery

Reference	Surgery	Anaesthesia technique	Patients	Survival	Criteria
Lin A *et al.*[49] Retrospective analysis Cancer: ovarian adenoK Inclusion period 1994–2006	**Inclusion criteria** Not measured **Exclusion criteria** No follow-up Loss of files	143/234 patient candidates: 106 patients: epidural (LA) vs 37 patients: PCA morphine Duration: 48 hours	**Age in years [range]** Epidural: 45.7 [30–65] PCA: 48.1 [32–68] **ASA 3–4:** Epidural: 2 PCA: 1 **FIGO III–IV score** Epidural: 57/106 PCA: 26/37	**Life duration in 2008** (survival 2–14.5 years) **Survival after 3 years** Epidural: 78% [IC95 70–86%] PCA: 58% [IC95 42–74%] **Survival after 5 years** Epidural: 61% [IC95 52–71%] PCA: 49% [IC95 32–65%]	Mortality at 3 years and 5 years **Methods used** Multifactor analysis Propensity score Kaplan–Meier
de Oliveira *et al.*[48] Retrospective analysis Cancer: ovarian 50% invasive Inclusion period 2000–2006	**Inclusion criteria** Hysterectomy with neoplasic reduction **Exclusion criteria** Benign tumours or tumours impossible to reduce surgically	182/232 patient candidates: 29 patients: GA + PE 26 patients: GA + PPE 127 patients: GA + PCA morphine Duration: 48–72 hours	**Age in years** PE: 55 (12) PPE: 55 (12) PCA: 57 (12) **ASA 3–4** PE: 7/29 PPE: 3/26 PCA: 36/127 **FIGO III-IV score** PE: 23/29 PPE: 16/26 PCA: 87/127 **Total IV opiates (mg) [95th percentile]** PE: 30 [15–42] PPE: 45 [28–65] PCA: 78 [54–120]	-	Follow-up for 3–9 years Recurrence diagnosed by CT scan or CA-125 > 21 U/ml **Kaplan–Meier (120 months)** *No recurrence:* PPE > PE > PCA ($P = 0.001$–0.002) *No recurrence FIGO III*: PPE > PCA ($P = 0.02$)

TABLE 2 Continued

Reference	Surgery	Anaesthesia technique	Patients	Survival	Criteria
Ismail *et al.*[50] Retrospective analysis Cancer: cervical Inclusion period 1996–2003	**Inclusion criteria** Uteral cervical cancer	132 patient candidates: 63 patients: epidural or spinal anaesthesia 69 patients: GA	**Age in years [95th percentile]** Peripheral nerve block: 61 [22–93] GA: 56 [27–85] **ASA 3–4** RA peripheral nerve block: 22/63 GA: 17/69 **Perioperative opioids** Peripheral nerve block: 20/63 GA: 69/69 **FIGO III-IV score** Peripheral nerve block: 14/63 GA: 22/69	-	**Kaplan–Meier probability of survival without recurrence (120 months)** GA vs truncal RA, $P = 0.863$ (ns) **Multifactor analysis** Recurrence risk factors: Type of tumour cells FIGO score tumour volume
Exadactylos *et al.*[40] Retrospective analysis Cancer: breast Inclusion period: 2001–2002	**Inclusion criteria** Mastectomy ± axillary resection **Exclusion criteria** Local tumour Sentinel node	129/194 patient candidates 50 patients: GA + PV block T2–T3, levobupivacaine 79 patients: GA + PCA morphine Duration: 48 hours	**Age in years [95th percentile]** PV block: 57 [51–64] PCA: 56 [50–64] **Pain** *At 4 hours* PV block: 1 [0–3] PCA: 3[2–5] *At 24 hours* PV block: 1 [0–2] PCA: 2[0–4] **Histology Grade III** PV block: 21/50 PCA: 42/79	1 patient died in the PCA group	**Metastases or recurrences in** **May 2005** (follow-up 2.5–4 years) PV block: 3/50 patients PCA: 19/79 patients **Kaplan–Meier (36 months)** No recurrence ParaV > PCA ($P = 0.013$)
Biki *et al.*[41] Retrospective study Cancer: prostate Inclusion period: 1994–2003	**Inclusion criteria** Prostatectomy **Exclusion criteria** Unknown	123 patients: GA + epidural T11–12 102 patients: GA + PCA morphine Duration: 48–72 hours	**Age in years** Epidural: 62 PCA: 63 **ASA 3–4** Epidural: 3/123 PCA: 8/102 **PSA** Epidural: 8 [6–13.6] GA: 8.7 [6.4–12.2]	-	Recurrence: PSA + Kaplan–Meier: no recurrence Epidural > PCA $P < 0.001$ **Multifactor analysis** Fewer recurrences if epidural vs GA No relation, but low Gleason score No invasion PSA preoperative Propensity score

TABLE 2 Continued

Reference	Surgery	Anaesthesia technique	Patients	Survival	Criteria
Tsui *et al.*[42] Retrospective study based on prospective Cancer: prostate Inclusion period: 2000–2001	**Inclusion criteria** Prostatectomy for cancer **Exclusion criteria** Unknown	99/102 patient candidates 49 patients: GA + epidural 50 patients GA + PCA morphine	**Age in years** Epidural: 63 (5.5) GA: 63.9 (6.1) **PSA** Epidural: 10.5 (8.2) GA: 63.9 (6.1)	One death due to cancer Four deaths not due to cancer in the epidural group control group: four deaths	PCA > 0.2 ng/ml and clinical recurrences No difference Epidural 11/49 GA 17:50
Wuethrich *et al.*[43] Retrospective analysis Cancer: prostate Inclusion period: 1994–2000	**Inclusion criteria** Unknown **Exclusion criteria** Unknown	261/307 patient candidates 103 patients: GA + thoracic epidural T10–T12 158 patients: GA + PCA morphine Duration: 48 hours	**Age in years** Epidural: 63 [57–67] GA: 64 [59–68] **ASA III** Epidural: 19/103 GA: 17/158 **PSA** Epidural: 12.3 [7.5–21.9] GA: 11 [7–17.1] **Perioperative fentanyl (mg)** Epidural 0.30 [0.2–0.50] GA: 0.70 [0.55–0.80]	-	PSA > 0.2 ng/ml Propensity score GA + epidural increases the rate of survival (HR: 0.45; IQR: 0.27–0.75) No difference in recurrence or mortality due to cancer

ASA, Physical Status Classification System; CA-125, cancer antigen 125; CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics; GA: general anaesthesia; HR, hazard ratio; IQR, interquartile range; LA, local anaesthesia; ns, not significant; PCA, patient-controlled analgesia; PE, postoperative epidural; PPE, peri- and postoperative epidural; PSA, prostate-specific antigen; PV, paravertebral; RA, regional analgesia.

References

1 Eschwege P, Dumas F, Blanchet P, *et al.* Haematogenous dissemination of prostatic epithelial cells during radical prostatectomy. *Lancet* 1995; 346:1528–30. http://dx.doi.org/10.1016/S0140-6736(95)92054-4

2 Foss OP, Brennhovd IO, Messelt OT, Efskind J, Liverud K. Invasion of tumour cells into the bloodstream caused by palpation or biopsy of the tumour. *Surgery* 1966; 59:691–5.

3 Denis MG, Lipart C, Leborgne J, *et al.* Detection of disseminated tumour cells in peripheral blood of colorectal cancer patients. *Int J Cancer* 1997; 74:540–4. http://dx.doi.org/10.1002/(SICI)1097-0215(19971021)74:5<540::AID-IJC11>3.0.CO;2-A

4 Holmgren L, O'Reilly MS, Folkman J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nat Med* 1995; 1:149–53. http://dx.doi.org/10.1038/nm0295-149

5 Shakhar G, Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: could they reduce recurrence rates in oncological patients? *Ann Surg Oncol* 2003; 10:972–92. http://dx.doi.org/10.1245/ASO.2003.02.007

6 Smyth MJ, Godfrey DI, Trapani JA. A fresh look at tumour immunosurveillance and immunotherapy. *Nat Immunol* 2001; 2:293–9. http://dx.doi.org/10.1038/86297

7 Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. *Nat Rev Cancer* 2003; 3:453–8. http://dx.doi.org/10.1038/nrc1098

8 Forget P, De Kock M. [L'anesthésie, l'analgésie et la modulation sympathique augmentent-elle l'incidence des récidives néoplasiques après chirurgie? Une revue de la littérature centrée sur la modulation de l'activité des lymphocytes natural killer.] *Ann Fr Anesth Reanim* 2009; 28:751–68. http://dx.doi.org/10.1016/j.annfar.2009.07.078

9 Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben- Eliyahu S. Attenuation of the tumour-promoting effect of surgery by spinal blockade in rats. *Anaesthesiology* 2001; 94:1066–73. http://dx.doi.org/10.1097/00000542-200106000-00022

10 Ben-Eliyahu S, Page GG, Yirmiya R, Shakhar G. Evidence that stress and surgical interventions promote tumour development by suppressing natural killer cell activity. *Int J Cancer* 1999; 80:880–8. http://dx.doi.org/10.1002/(SICI)1097-0215(19990315)80:6<880::AID-IJC14>3.0.CO;2-Y

11 Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumour-promoting effects of surgery in rats. *Pain* 2001; 90:191–9. http://dx.doi.org/10.1016/S0304-3959(00)00403-6

12 Wong IH, Lau WY, Leung T, Yeo W, Johnson PJ. Haematogenous dissemination of hepatocytes and

tumour cells after surgical resection of hepatocellular carcinoma: a quantitative analysis. *Clin Cancer Res* 1999; 5:4021–7.

13 Zetter BR. Angiogenesis and tumour metastasis. *Annu Rev Med* 1998; 49:407–24. http://dx.doi.org/10.1146/annurev.med.49.1.407

14 O'Reilly MS, Holmgren L, Shing Y, *et al.* Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. *Cell* 1994; 79:315–28. http://dx.doi.org/10.1016/0092-8674(94)90200-3

15 O'Reilly MS, Boehm T, Shing Y, *et al.* Endostatin: an endogenous inhibitor of angiogenesis and tumour growth. *Cell* 1997; 88:277–85. http://dx.doi.org/10.1016/S0092-8674(00)81848-6

16 Folkman J. Tumour angiogenesis. In: Mendelsohn J, Howley PM, Israel MA, Liotta LA, editors. *The Molecular Basis of Cancer*. WB Saunders; 1995.

17 Lutgendorf SK, Cole S, Costanzo E, *et al.* Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. *Clin Cancer Res* 2003; 9:4514–21.

18 Antoni MH, Lutgendorf SK, Cole SW, *et al.* The influence of biobehavioural factors on tumour biology: pathways and mechanisms. *Nat Rev Cancer* 2006; 6:240–8. http://dx.doi.org/10.1038/nrc1820

19 Sacerdote P, Bianchi M, Gaspani L, *et al.* The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesth Analg* 2000; 90:1411–4. http://dx.doi.org/10.1097/00000539-200006000-00028

20 Brand JM, Kirchner H, Poppe C, Schmucker P. The effects of general anaesthesia on human peripheral immune cell distribution and cytokine production. *Clin Immunol Immunopathol* 1997; 83:190–4. http://dx.doi.org/10.1006/clin.1997.4351

21 Markovic SN, Knight PR, Murasko DM. Inhibition of interferonstimulation of natural killer cell activity in mice anesthetized with halothane or isoflurane. *Anaesthesiology* 1993; 78:700–6. http://dx.doi.org/10.1097/00000542-199304000-00013

22 Shapiro J, Jersky J, Katzav S, Feldman M, Segal S. Anaesthetic drugs accelerate the progression of postoperative metastases of mouse tumours. *J Clin Invest* 1981; 68:678–85. http://dx.doi.org/10.1172/JCI110303

23 Melamed R, Bar-Yosef S, Shakhar G, *et al.* Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. *Anesth Analg* 2003; 97:1331–9. http://dx.doi.org/10.1213/01.ANE.0000082995.44040.07

24 Zhou W, Fontenot HJ, Wang SN, Kennedy RH. Propofol-induced alterations in myocardial beta-adrenoceptor binding and responsiveness. *Anesth Analg* 1999; 89:604–8.

25 Beilin B, Shavit Y, Hart J, *et al.* Effects of anaesthesia based on large versus small doses of fentanyl on natural killer cell cytotoxicity in the perioperative period. *Anesth Analg* 1996; 82:492–7.

26 Yeager MP, Colacchio TA, Yu CT, *et al.* Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. *Anaesthesiology* 1995; 83:500–8. http://dx.doi.org/10.1097/00000542-199509000-00008

27 Gupta K, Kshirsagar S, Chang L, *et al.* Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signalling and promotes breast tumour growth. *Cancer Res* 2002; 62:4491–8.

28 Shavit Y, Lewis JW, Terman GW, Gale RP, Liebeskind JC. Opioid peptides mediate the suppressive effect of stress on natural killer cell cytotoxicity. *Science* 1984; 223:188–90. http://dx.doi.org/10.1126/science.6691146

29 Gaveriaux-Ruff C, Matthes HW, Peluso J, Kieffer BL. Abolition of morphine-immunosuppression in mice lacking the mu-opioid receptor gene. *Proc Natl Acad Sci U S A* 1998; 95:6326–30. http://dx.doi.org/10.1073/pnas.95.11.6326

30 Page GG, Ben-Eliyahu S, Yirmiya R, Liebeskind JC. Morphine attenuates surgery-induced enhancement of metastatic colonization in rats. *Pain* 1993; 54:21–8. http://dx.doi.org/10.1016/0304-3959(93)90095-7

31 Kehlet H. The stress response to surgery. In: Cousins MJ, Brindenbaugh PO, editors. *Neural Blockade in Clinical Anaesthesia and Management of Pain*. New York, NY: Lippincott Williams, Wilkins; 1998.

32 Buggy DJ, Smith G. Epidural anaesthesia and analgesia: better outcome after major surgery? Growing evidence suggests so. *BMJ* 1999; 319:530–1. http://dx.doi.org/10.1136/bmj.319.7209.530

33 Sakaguchi M, Kuroda Y, Hirose M. The antiproliferative effect of lidocaine on human tongue cancer cells with inhibition of the activity of epidermal growth factor receptor. *Anesth Analg* 2006; 102:1103–7. http://dx.doi.org/10.1213/01.ane.0000198330.84341.35

34 Martinsson T. Ropivacaine inhibits serum-induced proliferation of colon adenocarcinoma cells *in vitro*. *J Pharmacol Exp Ther* 1999; 288:660–4.

35 Jose C, Bellance N, Chatelain EH, Benard G, Nouette-Gaulain K, Rossignol R. Antiproliferative activity of levobupivacaine and aminoimidazole carboxamide ribonucleotide on human cancer cells of variable bioenergetic profile. *Mitochondrion* 2012; In press

36 Wada H, Seki S, Takahashi T, *et al.* Combined spinal and general anaesthesia attenuates liver metastasis by preserving T_h1/T_h2 cytokine balance. *Anaesthesiology* 2007; 106:499–506. http://dx.doi.org/10.1097/00000542-200703000-00014

37 Kurosawa S Anaesthesia in patients with cancer disorders. *Curr Opin Anaesthesiol*. 2012; 25:376–84. http://dx.doi.org/10.1097/ACO.0b013e328352b4a8

38 Beloeil H, Nouette-Gaulain K.The perioperative period in cancer surgery: A critical moment! Is there a role for regional anaesthesia in preventing cancer recurrence? *Ann Fr Anesth Reanim*. 2012; 31:528–36. http://dx.doi.org/10.1016/j.annfar.2012.01.037

39 Schlagenhauff B, Ellwanger U, Breuninger H, Stroebel W, Rassner G, Garbe C. Prognostic impact of the type of anaesthesia used during the excision of primary cutaneous melanoma. *Melanoma Res* 2000; 10:165–9.

40 Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anaesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anaesthesiology* 2006; 4:660–4. http://dx.doi.org/10.1097/00000542-200610000-00008

41 Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anaesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anaesthesiology* 2008; 109:180–7. http://dx.doi.org/10.1097/ALN.0b013e31817f5b73

42 Tsui BCH, Rashiq S, Schopflocher D, *et al.* Epidural anaesthesia and cancer recurrence rates after radical prostatectomy. *Can J Anesth* 2010; 57:107–112. http://dx.doi.org/10.1007/s12630-009-9214-7

43 Wuethrich PY, Hsu Schmitz SF, Kessler TM, *et al.* Potential influence of the anaesthetic technique used during open radical prostatectomy on prostate cancer-related outcome: a retrospective study. *Anaesthesiology* 2010; 113:570–6.

44 Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anaesthesia. *Anesth Analg* 2008; 107:325–32. http://dx.doi.org/10.1213/ane.0b013e3181770f55

45 Gottschalk A, Ford JG, Regelin CC, *et al.* Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. *Anaesthesiology* 2010; 113:27–34. http://dx.doi.org/10.1097/ALN.0b013e3181de6d0d

46 Gupta A, Bjornsson A, Fredriksson M, Hallbook O, Eintrei C. Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in central Sweden. *Br J Anaesth* 2011; 107:164–70. http://dx.doi.org/10.1093/bja/aer100

47 Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomized trial. *BMJ* 2011; 342:d1491. http://dx.doi.org/10.1136/bmj.d1491

48 de Oliveira GS, Jr., Ahmad S, *et al.* Intraoperative neuraxial anaesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. *Reg Anesth Pain Med* 2011; 36:271–7. http://dx.doi.org/10.1097/AAP.0b013e318217aada

49 Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. *Br J Anaesth* 2011; 106:814–22. http://dx.doi.org/10.1093/bja/aer055

50 Ismail H, Ho KM, Narayan K, Kondalsamy-Chennakesavan S. Effect of neuraxial anaesthesia on tumour progression in cervical cancer patients treated with brachytherapy: a retrospective cohort study. *Br J Anaesth* 2010; 105:145–9. http://dx.doi.org/10.1093/bja/aeq156

51 Montélimard A MF, Nourissat A, Zufferey P, Molliex S. Can cervical epidural anaesthesia improve survival in head and neck cancer surgery? ASA abstract 2010; A017.

52 Sessler DI. Long-term consequences of anaesthetic management. *Anaesthesiology* 2009; 111:1–4. http://dx.doi.org/10.1097/ALN.0b013e3181a913e1

53 Arain MR, Buggy DJ. Anaesthesia for cancer patients. *Curr Opin Anaesthesiol* 2007; 20:247–53. http://dx.doi.org/10.1097/ACO.0b013e32814f1c34