Compendium

Anaesthesia in Surgical Oncology

Michael Šrámek

The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital

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Department of Anesthesiology, Intensive Care and Pain Medicine
Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital
Amsterdam

Academic Staff:

Mrs. Karin Ariese-Beldman, MD
Mrs. Marloes Bolman, MD
Dirk Buitelaar, MD
Mrs. Sannine Buma, MD
Mrs. Julia ten Cate, MD
Mrs. Katrina Efthymiou, MD
Christoph Hahn, MD, PhD
Mrs. Lenie Hulshoff, MD
Mrs. Sandra Huissoon, MD
Mrs. Anne Lukas, MD, PhD
Mrs. Anita Rothengatter-Ophof, MD
Peter Schutte, MD
Michael Šrámek, MD, PhD
Mrs. Ingeborg Vergouwe, MD
Dick Visser, RN, MANP
Mrs. Marchien van der Weide, MD, PhD
Mrs. Esther Wolthuis, MD, PhD

Summary

Recently there has been growing interest in the relationship between anaesthesia and surgical oncology, particularly in its possible effects on cancer recurrence. Increasing evidence shows that not only surgical intervention influences tumour growth and metastasis, but that anaesthetics and anaesthetic techniques also might influence tumour development. As we work in a hospital specially focused on the diagnosis and treatment of cancer we designed a compendium. This compendium is founded on an extended search for literature in which the relation between anaesthesia, surgical oncology and outcome was studied. Based on these study results we have formulated suggestions and recommendations. As far as possible, these recommendations have already been incorporated into our daily practice. Periodical renewal of the literature will be needed to ensure that the recommendations remain up to date, and will be modified when needed. In this way, we hope to contribute to giving the most appropriate care in surgical oncology.

Compendium – Anaesthesia in surgical Oncology

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I Introduction

As the population grows older, an evident increase in incidence of cancer is seen. Better diagnostics have led to earlier treatment and better survival. Since it has been shown that every tumour has its own unique identity, future treatment will focus on mutations in cancer cell DNA, making specific and individual treatment possible. This will hopefully result in converting more types of cancer into a chronic disease.
Despite this recent development, surgery still takes a leading part in the treatment of cancer. Obviously, (major) surgery cannot be performed without anaesthesia. There is growing appreciation that even a short-term event such as the perioperative period can have its influence on the oncological process as a whole. Presently, effects on the so-called Minimal Residual Disease, the role of inflammation and the various transitions are at the centre of interest.

For more comprehensive background information on (surgical) oncology we refer to the numerous textbooks available. Although many underlying mechanisms have been unveiled, the exact interaction between the perioperative period and the following oncological process has not been completely clarified yet. The following study results will illustrate that many factors may be of influence.
For instance, it has been shown that immunity is significantly suppressed in the perioperative period. This suppression is a result of both neuroendocrine and cytokine stress response systems (1). Obviously, the suppression of immunity is a complex and multifactorial process (2). Lewis et al demonstrated that pain itself is capable of promoting tumour growth (3). In addition, Bar-Yosef and his colleagues have demonstrated that pain can also lead to an increase in metastases (4).

The cellular immunosuppression evoked by surgical stress proves to last for several days in case major surgery is involved (5). As demonstrated by Coffey and co-workers, humoral immunity remains relatively intact, whilst peak levels in cellular immunosuppression are encountered around the third day postoperatively (6). It appears that the level of immunosuppression is also determined by the degree of tissue damage caused by the surgical intervention. A laparoscopy proves to be less immunosuppressive than a

laparotomy (7). Animal research in mice has shown that increased surgical stress leads to an increase in metastases (8).

Many events in the treatment of cancer fall outside the scope of the anaesthesiologist. However, within the perioperative period the anaesthesiologist has the potential to play a pivotal role. The aim of this compendium is to offer an overview of results from scientific literature, focusing specifically on the relationship between the perioperative process and its influence on growth and recurrence of cancer. By doing so, we hope to offer a guideline through which a justified choice can be made for specific anaesthesia techniques and anaesthetics in oncological surgery.

In the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital in Amsterdam, emphasis is placed on diagnostics and treatment of most (solid) tumours. Overall, one could say that the major difference between the male and female patient population lies in the incidence of the most commonly encountered tumour: breast cancer in female patients and cancer of the prostate in male patients.

Apart from ascertaining that the patient undergoes the operation as well as possible, the anaesthesiologist can contribute further by making sure the patient receives oncological sound perioperative care by:

- restraining both the internal and surgical stress response,
- choosing the most appropriate anaesthetic technique,
- choosing the most appropriate anaesthetics,
- avoiding hypothermia.

Apart from the fact that pain and surgery appear to play a role in suppressing immunity, and consequently may be of influence on the oncological process, there are several indications that the anaesthetics and pharmaceuticals administered during surgery can be of influence on tumour progression and cancer recurrence (9,10,11). In his article, Snyder shows a clear overview on pathogenesis of tumour metastases, the response of an intact immune system to

the presence of tumour cells and the effect of surgery on endogenous defence mechanisms and the formation of metastases (10).

The anaesthesia technique and used anaesthetics can affect the oncological process in many ways. In principle, all revolves around the mutation of the equilibrium between endogenous immunity and potency of the tumour (tumour growth as well as potency of metastasizing):

- Endogenous cellular immunity. Natural Killer (NK) cells play an important role in cellular immunity. It has been demonstrated that patients with lower NK-cell activity have a higher incidence of malignancies (12). Several studies also show NK-cell activity at the time of surgery being inversely proportional to the development of metastases. Stress (including surgical stress) can lead to a stress-induced decrease of NK-cell activity. Animal research has shown that this reduced NK-cell activity can result in more rapid tumour growth (13). Page GG et al demonstrated that postoperative pain solely is able to act as a mediator for tumour enhancing effects of surgery in rats (14).

Interleukin-2 (IL2) and interferon-gamma (IFNγ) are important activators of NK-cell activity. Cytotoxic T cells also play a part in immunity. The main hypothesis is that autonomous cellular immunity plays an important role in the process of metastasizing (beginning at minimal residual disease).

- Tumour cell proliferation and angiogenesis. Important mediators in these processes are Vascular Epidermal Growth Factor (VEGF) and prostaglandin E2.
Morphine has demonstrated to have pro-angiogenic properties and hence the ability to increase tumour growth in research animals, in case of breast cancer (15).

The relation between perioperatively frequently used pharmaceuticals and their effect on cellular immunity, tumour cell proliferation and angiogenesis has also been studied. As shown in the following summary, the use of most of these pharmaceuticals results in decreased NK-cell activity and/or number of NK-cells. The extent to which this finding bears clinical relevance will be discussed later on in the compendium. A striking finding was that of all studied local anaesthetics none seemed to have an effect on NK-cell activity.

However, they did appear to have an inhibiting effect on tumour cell proliferation and tumour growth in vitro.

Pharmacon	Potential effect on anti tumour host immunity
Thiopental	decreased NK-cell activity and cell number (AM)
Propofol	decreased NK-cell number (AM)
Volatile anaesthetics	inhibition of interferon stimulation by NK-cell toxicity (AM) Decreased NK-cell number in humans*
Nitrous Oxide	associated with accelerated manifestation of lung and liver metastases (AM) no effect on surgical outcome in colorectal carcinoma in humans inhibits generation of hematopoietic cells (of possible importance for tumour cells)
Local anaesthetics	lidocaine: inhibition of tumour cell proliferation in vitro ropivacaine: inhibition of tumour cell growth in vitro
Morphine	inhibition of cellular immunity, including NK-cell activity (AM and HM)
Fentanyl	inhibition of NK-cell activity (HM)
Tramadol	stimulation of cellular immunity, including NK-cell activity (AM and HM)
COX-2 inhibitors	expression of anti-angiogenesis and anti-tumour properties (AM)
S-Ketamine	decreased NK-cell activity and cell number (AM)

AM: animal model/experiment
HM: human model
* associated with worse outcome when compared to local infiltration in excision of melanoma
(from Snyder GL, et al.(10).

Propofol

Propofol appears to take a particular position. Although propofol is known to display protective anti-oxidative properties, probably due to the haem-oxygenase enzyme (HO-1), its effects on cancer are less clear. In some studies, the use of propofol is reported to have a

potentially adverse effect on cancer. Garib et al, for instance, demonstrated that propofol increased migration of breast cancer cells due to activation of GABA (16). On the other hand, other studies reported propofol to have protective effects by inhibiting invasion of human colonic cancer cells (17,18).

These contrary results made Zhang study the effects of propofol on gallbladder carcinoma. He found that the use of propofol was associated with a (dose dependent) increase of proliferation and invasion of gallbladder cancer cells. This finding was explained by both inhibition of apoptosis and amplification of invasive abilities (19).

Song et al. report that propofol exhibits anti-cancer effects by promoting apoptosis (20). Su and colleagues confirm that propofol can effectively inhibit proliferation and induce apoptosis of human epithelial ovarian cancer cells (21). Zhang et al. demonstrate that propofol exhibits anti-tumour effects by inhibiting growth of human hepatocellular cancer cells (22).

Based on the results of a prospective study, in which the effects of propofol, isoflurane and enflurane on interleukin-8 (IL-8) and IL-10 levels in cancer patients were studied, Liu concludes that propofol can be regarded as a preferable anaesthetic agent compared with isoflurane and enflurane. This conclusion is based on the fact that propofol was able to inhibit serum IL-8 secretion and to improve IL-10 secretion to a greater extent than isoflurane and enflurane. In other words, improved secretion of anti-inflammatory cytokine(s) and less secretion of pro-inflammatory cytokine(s), resulting in inhibition of the surgical inflammatory stress response (23).

Volatile anaesthetics

As for the use of volatile anaesthetics, study results may be a little less unclear. Although there is some evidence that halogenated volatile anaesthetics behave organ-protective against ischemia (24), in vitro research has demonstrated that isoflurane and halothane both have an indirect inhibiting effect on NK-cell activity. Sevoflurane has been shown to have an effect on the release of cytokines, including IL1β and TNFα (25, 26). Furthermore, Kawaraguchi et al have shown that colon cancer cells are protected by isoflurane. The mechanism responsible for this protection is thought to be an acquired resistance against TNF-related apoptosis (27).

Miyata et al. have studied the effects of general anaesthesia with isoflurane following propofol induction on natural killer cell cytototoxic activities of peripheral blood lymphocytes in dogs. They report that a significant decrease in NK-cell activity was observed at 24 hours after anaesthesia. The NK cytotoxic activities were recovered to the baseline values until 120 hours after the anaesthesia (28).

There is lack of solid research on the effects of volatile anaesthetics. However, a large retrospective study in melanoma patients showed that the use of volatile anaesthetics, as part of general anaesthesia, resulted in worse survival compared to the use of local anaesthetics only (29). By contrast, Lindholm's study revealed no increased incidence of new malignant disease in patients anaesthetized with sevoflurane. In this study, neither the duration of sevoflurane anaesthesia or its depth appeared to be of influence (30).

Based on their in vitro study, Ecimovic and colleagues report that sevoflurane increases proliferation, migration and invasion in estrogen receptor-positive breast cancer cells (ER(+)), and proliferation and migration, but not invasion, in estrogen receptor-negative breast cancer cells (ER(-)). Albeit, the observed effect size was small and not dose-dependent (31).

Huang et al. claim that there is strong evidence that isoflurane should not be used in prostate cancer surgery, in contrast to propofol. This claim is based on the finding that isoflurane enhances cancer cell characteristics associated with malignancy in exposed prostate cancer cells. In other words, prostate cancer cell line (PC3) exposed to isoflurane showed characteristics associated with malignancy with an increase of proliferation and migration, as well as development of chemoresistance. Exposure to propofol, on the other hand, resulted in partial reduction of cancer cell malignant activities (32).

Jaura cum suis claim that sevoflurane anaesthesia combined with opioid analgesia for primary breast cancer surgery reduces apoptosis in oestrogen receptor (ER)-negative breast cancer cells to a greater extent than propofol anaesthesia combined with paravertebral analgesia. In this prospective randomized clinical trial patients with biopsy-proven ER (-) breast cancer received either sevoflurane anaesthesia combined with opioid analgesia or

propofol anaesthesia with paravertebral analgesia during surgery. Blood was drawn and serum was exposed to ER (-) MDA-MB-231 cells. Apoptosis was measured using ApoLive-Glo Multiplex Assay. Based on the results, they conclude that anaesthetic technique may affect the composition of serum in a manner that impacts cancer cell apoptosis, and consequently tumour metastasis (33).

In contrast to this study, other studies show opposite results. Muller-Edenborn reports that sevoflurane and desflurane inhibit migration of colorectal cancer cells in vitro (34). This inhibitory effect is caused by the reduction of release of matrix metalloproteinase-9 (MMP-9) by neutrophils. Liang reports the same finding with respect to lung cancer cells (35). Elias et al. even claim that the use of desflurane in ovarian cancer patients undergoing cytoreductive surgery is associated with improved disease-free survival compared with other volatile anaesthetics (437).
Nonetheless, Marana and co-workers report that desflurane and sevoflurane produce a different stress response in the setting of laparoscopic surgery. Based on their prospective randomized study, in which patients undergoing laparoscopic surgery for benign ovarian cyst were studied, the authors claim that desflurane anaesthesia results in a higher release of the catecholamines epinephrine and norepinephrine compared to sevoflurane anesthesia. However, both vapours did not influence the plasmatic levels of Interleukin -6, CRP and glucose (36). The clinical significance of these findings remains unclear.

With respect to the analgesic requirements after anaesthesia with volatile anaesthetics, Fassoulaki and colleagues report that opioid consumption and pain 24 hours postoperatively does not differ among postoperative patients undergoing abdominal hysterectomy under sevoflurane, desflurane or propofol anaesthesia (37).

Nitrous oxide

Nitrous oxide appears to both slow neutrophil function and decrease mononuclear cell proliferation. A study in mice associated the use of nitrous oxide with an increased manifestation of lung and liver metastases (38). However, in another study on colorectal

carcinoma, the use of 65% nitrous oxide did not result in higher cancer recurrence, with follow up of the patients for a period of 4 to 8 years (39).

Local anaesthetics

Local anaesthetics, like lidocaine and ropivacaine, appear to inhibit proliferation as well as growth of cancer cells in vitro (40). Lidocaine showed a distinct anti-tumour effect in an in vitro study in human tongue carcinoma (41). Other studies have confirmed these findings (42, 43). Strikingly, Piegeler demonstrated that only local anaesthetics of the amide type display these inhibiting properties, in contrast to local anaesthetics of the ester type (44).

It has to be mentioned, however, that Lirk and colleagues have shown that lidocaine and ropivacaine, but not racemic bupivacaine, demethylate deoxyribonucleic acid in breast cancer cells in vitro. Decrease in methylation has been shown to reactivate tumour suppressor genes and therefore to inhibit tumour growth. In that view, one could advocate the use of ropivacaine rather than bupivacaine when locoregional techniques are considered in surgical oncology (45). These “anti-inflammatory” effects are believed to be independent of sodium channel inhibition.

Ramirez et al. report that clinically relevant concentrations of lidocaine enhance the in vitro function of NK-cells via the release of lytic granules (46).

In their paper, Votta-Velis and colleagues address the relation between inflammation, cancer and amide-linked local anaesthetics (47).

Opioids

Opioids administered both peroperatively and chronically display evident effects on both cellular and humoral immunity (48-49). These effects include decreased NK-cell activity, production of immunity stimulating cytokines, phagocytic activity and production of antibodies (50). Morphine has been shown to have the potency to suppress cytotoxicity of NK-cells in rats in a dose dependent way. This suppression proved sensitive to naloxone, meaning that by administering naloxone the suppressing effect of morphine could be undone (51). A breast cancer study in mice showed that administration of morphine resulted

in an increase in angiogenesis and more rapid tumour growth (15). Markedly, this morphine effect could be undone by administering celecoxib without abolishing its analgesic effects (52).

It has been demonstrated in both animal and human studies that opioids also suppress NK-cell cytotoxicity postoperatively. This effect appears to persist for a longer period of time when higher doses of opioids (fentanyl) are administered. Strikingly, this NK-cell suppression proved completely reversible by human recombinant IL-2 en partially reversible by IFN-α and IFN-β (53). In a study in rats undergoing laparotomy, Page and colleagues established that morphine administered pre-operatively resulted in less immune suppression than morphine administered at a later moment in surgery. This could be explained by prevention, respectively early inhibition of pain related neuroendocrine responses. This finding is highly suggestive for a kind of preemptive mechanism (54).

Although there is ample evidence that opioids exert a favourable effect on restraining the inflammatory stress response caused by the surgical procedure, evidence is growing that opioids also may exert unfavourable effects through immunomodulation.

In their retrospective study, Cata and colleagues report that intraoperative opioid use is associated with decreased overall survival in stage I, but not in stage II or III non-small cell lung cancer (55).
Maher et al. also suggest an association between increased doses of opioids during the initial 4-day postoperative period with a higher recurrence rate of non-small-cell lung cancer (56).

Based on their study results, Lennon and colleagues suggest a possible direct effect of Mu Opioid Receptor (MOR) stimulation on opioid and growth-factor-induced proliferation, migration and epithelial mesenchymal transition (EMT) in human lung cancer. They demonstrate that the peripheral mu opioid receptor antagonist, methylnatrexone, inhibits epidermal growth factor-induced proliferation and migration of human lung cancer cells in a dose-dependent manner. Morphine, on the other hand, was shown to promote cell proliferation and invasion of human lung cancer cells (57). These findings are supported by

previous study (58). Furthermore, they conclude that pain and inflammation may promote epithelial mesenchymal transition (EMT) in cancer cells through Substance-P transactivation of MOR.

For the purpose of clarification, epithelial mesenchymal transition (EMT) and mesenchymal epithelial transition (MET) are recognized as critical components in the sequential series of events resulting in metastasis of carcinomas. This is well illustrated in the papers by Thiery and Yao (59,60). EMT and MET are defined as changes in cell phenotype between the epithelial and mesenchymal states. To simplify, solid tumour progression involves spatial and temporal occurrences of EMT, through which tumour cells acquire a more invasive and metastatic phenotype. Once the mesenchymal tumour cells have successfully disseminated, they undergo the reverse transition, MET, at the site to which they have disseminated. In other words, EMT is thought to be essential for the initial transformation from benign to invasive carcinoma, whereas MET is held essential for the latter stages of metastasis. The factors, that induce either MET or EMT are believed to be components of different signalling pathways that originate in the tumour's own local environment from stroma cells. Depending on the type of signal, mainly influenced by the tumour's own local environment, either MET or EMT is induced. This local microenvironment is furthermore influenced by the presence, or indeed absence, of certain cytokines and inflammatory cells.

In both animal and human models, it has been documented that removal of a primary tumour may result in a reduction of inhibition of angiogenesis, and that surgery is followed by a surge in cytokine production that promotes angiogenesis and growth factors aiding wound healing (61-63).

Therefore it is not surprising that tumour angiogenesis and proliferation may be provoked by the surgery involved in the attempt to control the primary tumour. Surgery itself could thus be responsible for the awakening of dormant metastases. This hypothesis is supported by the study performed by Chang and colleagues. In their study, they show that "normal wound healing" may very well play an important role in cancer metastasis. They base this on the fact that in a series of 295 early breast cancer patients, both overall survival and distant metastasis-free survival were markedly diminished in patients whose tumours

expressed this, what they call, wound-response signature compared to tumours that did not express this signature (64).

In summary, there is growing evidence that inflammation plays a key role in the development and recurrence of cancer. Malignant tumours have been shown to induce inflammation and subsequently to initiate anti-tumour responses, which are mainly cellularly mediated. This endogenous defence system has the potency to recognize cancer cells in an early stage and to generate the production of inflammatory cytokines. These, on their turn, attract immune cells, such as lymphocytes, macrophages and dendritic cells. In this way, inflammation "protects" the body from cancer cells.
On the other hand, inflammation has also been shown to be able to induce carcinogenesis, dedifferentiation and primary tumour growth, prior to dissemination. After dissemination, the inflammatory process has the potential to promote the proliferation of tumour cells by inhibition of apoptosis and by increasing cell division (mitosis) (65).

Which processes are responsible for this paradox?
Overall, both surgery, inflammation and tumour growth facilitating mechanisms are closely linked.
When a tumour is surgically removed, tumour cells inevitably are released in the tumours vicinity due to manipulation of the tumour. The extent to which tumour cells successfully reach the blood stream is determined by the inflammatory microclimate in the vicinity of the primary tumour.
Apart from facilitating dissemination of tumour cells, the inflammatory process also has the ability to enhance the growth of metastases. Thrombocytes may be involved in the process of dissemination, partly through adhesive mechanisms, partly via the synthesis of mediators. In turn, immune cells on the one hand have the potential to contribute to the elimination of tumour cells (Natural Killer cells, cytotoxic T-lymphocytes and dendritic cells), on the other hand to suppress the immune response (T-regulating lymphocytes, tumour-associated macrophages, neutrophils and myeloid-derived suppressor cells). Tumour cells that escape the immune surveillance may thus lead to cancer recurrence or metastases (66).
For further information regarding inflammation and cancer we refer to the paper by Coussens and Werb (67).

The enzyme cyclooxygenase-2 appears to be over-expressed in both tumour cells and immune suppressor cells, like for instance macrophages. Prostaglandin E2, which is formed from arachidonic acid via the cyclooxygenase pathway, is capable of stimulating tumour growth, both directly and indirectly by suppressing cellularly mediated immunity.
The cytokines, interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-α) also possess the ability to suppress the activity of immune cells in a direct way, and to promote both the number of suppressor cells and their activity. This process is further exacerbated by other factors associated with tissue damage caused by surgery, such as additional release of (nor) epinephrine and cortisol (68-70).
In this regard, it may obvious that anaesthesia on its own, and/or by restraining the impact of surgery induced inflammatory stress response, has the potential to interfere with many of these processes (68,69).
For a more detailed overview on the relation between surgery, inflammation and cancer we refer to the paper by Roxburgh and colleagues (70).

To simplify, one could conclude that opioids have a clear effect on moderating surgical tissue damage, partly by altering pain perception and partly by attenuating several responses following surgical stress. As such, opioids have a modulating effect on autonomic defence mechanisms. Despite the fact that in vitro and animal studies have shown that morphine can a negative effect on these (cancer) defence mechanisms, it appears that opioids in general have a favourable effect on controlling surgical stress. Surgical stress without the use of opioids could therefore have a more adverse effect on tumour evolution than surgery with the perioperative use of opioids (71-73).

Tramadol

In contrast to morphine, tramadol exhibits different effects on autonomic immunity. Apart from its effects on opioid receptors, tramadol also influences the noradrenergic and serotonergic systems. In both rodent and human studies, a subsequent increase of NK-cell activity was noticed after treatment with tramadol (74). Furthermore, tramadol has been shown to prevent both surgically induced suppression of NK-cell activity as well as increase

of lung metastases. In a study, in which women with endometrial carcinoma underwent hysterectomy, administration of 100 mg tramadol immediately after the operation was shown to result in an increase in NK-cell activity (75).

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAID's) slow down prostaglandin synthesis by inhibiting the enzyme cyclooxygenase (COX). Various tumours have been shown to possess the ability of secreting prostaglandins. This could explain why in rat studies COX-2 inhibitors display anti-tumour and anti-angiogenic effects (76,77).

These anti-tumour and anti-angiogenic effects were also encountered in the perioperative setting in another rat study. In this study, the immunosuppressant effects caused by surgery were prevented by synergistically combining beta-blockade and COX-2 inhibition (78). The favourable effects caused by COX-2 inhibition are thought to be the result of prostaglandin synthesis, whilst the use of beta-blockade results in a lower release of catecholamines and subsequently a reduction in stress response (79-81). Several studies have demonstrated that COX-2 inhibitors in general, and diclofenac in special, display anti-tumour effects. Kaur showed that diclofenac has the ability to decrease angiogenesis in colon carcinoma (82,83). Johannesdottir demonstrated a preventive effect in certain skin tumours, including melanoma and basal cell carcinoma (84). Singh confirmed that diclofenac is able to induce apoptosis and differentiation in human acute myeloid leukaemia cells (85). Finally, Mayorek demonstrated comparable anti-tumour effects in pancreatic carcinoma (86).

Pitt states that some cancers generate heat internally, which results in a higher temperature in the cancer compared with surrounding tissue. This is termed excess entropy production in cancer. This excess entropy production is supposed to drive the cancer away from the stationary state that is characterized by minimum entropy production. Treatments that reduce inflammation, and therefore temperature, should be able to drive a cancer towards the stationary state, thus reducing the progress of cancer (87).

As discussed previously both surgery, inflammation and tumour growth facilitating mechanisms appear closely linked. Therefore, one has tried to investigate the possibility of identifying a screening tool that would enable to ascertain a patient's inflammatory status

preoperatively, in relation to the course of the immune response, both intra- and postoperatively (88-89).

Based on their prospective randomized trial in 35 patients with colon cancer, Moselli and colleagues claim that epidural analgesia attenuates the early and surgery-induced pro-inflammatory response and its typical postoperative immunosuppression, and that epidural analgesia appears to be associated with a reduced rate of postoperative complications compared with intravenous analgesia (90).

Bartal cum suis have demonstrated that a variety of immunological differences can be encountered in preoperative patients. In other words, preoperative patients differ from each other with respect to their immune status. The clinical significance of this difference in immune status has not been fully clarified yet. Nevertheless, it seems quite plausible that a patient's preoperative immune status will affect the way the body responds to surgical trauma. This holds also true for the way by which anti-inflammatory drugs exert their modulating effects (91). Forget and colleagues claim that inflammation is closely linked to worse outcome, and that even a single intra-operative administration of a non-steroidal anti-inflammatory drug, like for instance diclofenac, is able to counteract this adverse association (92). Especially, the expected prominent early relapse events in months 9-18 after breast surgery were reduced 5-fold.

Christopherson observed the same finding in his study involving colon carcinoma (93). In case of non-small cell lung cancer the use of diclofenac was associated with longer (distant) metastasis-free survival and longer overall survival.
Shebl et al. have conducted a prospective propensity matched cohort study, in which the relation between NSAID's use and cancer incidence was studied. In short, more than 314.000 participants were asked to complete a lifestyle questionnaire, which included NSAID use. Median follow-up of participants was 10.1 person-years. Information on cancer incidence was ascertained by linking to cancer registries and vital status databases. Results revealed that individuals who reported use in the 12 months prior to interview had a significantly lower risk of all inflammation-related cancers (alcohol-, infection-, obesity-,

and smoking-related cancer). These findings once more support the hypothesis that inflammation is related to an increased risk of certain cancers (94).

In connection with this, several studies have tried to identify a biomarker that would enable us to ascertain the immune status of the individual patient, in relation to the outcome of treatment. Multiple studies have identified the neutrophil-to-lymphocyte ratio (NLR) as a suitable tool (95-118). These studies demonstrate that a high preoperative NLR is associated with faster progression of the tumour and worse outcome.
Strikingly, in patients with breast cancer and a high preoperative NLR (≥ 4), the use of NSAID's was associated with a reduction of the relative risk of cancer recurrence and mortality by more than 50%, compared to patients with a NLR < 4. In other words, breast cancer patients with a high NLR, a higher inflammatory grade, profit most of the anti-inflammatory treatment with diclofenac. Once more, this finding illustrates the connection between (grade of) inflammation and tumour growth.

Furthermore, this would explain why certain tumours respond less to anti-inflammatory treatment than others. In contrast to a tumour with a higher inflammatory grade, a tumour with a lower rate of growth and potency to metastasize, and often with a lower inflammatory grade, is less likely to respond to treatment with NSAID's. Forget and colleagues, for instance, were not able to demonstrate any beneficiary effect of anti-inflammatory treatment on recurrence or survival in over 1000 patients undergoing radical prostatectomy (119).
Vidal et al. report that, based on the results of the REDUCE study, the use of aspirin and/or NSAID is significantly associated with decreased total and high-grade prostate cancer risk, but not with low-grade prostate cancer risk (120). This supports the theory that low-grade cancers/cancers in patients with a low NLR, are less likely to respond to anti-inflammatory treatment. Inversely, high-grade cancers/cancers in patients with a high NLR are more likely to respond to treatment with NSAID's.

In brief, it appears that the grade of inflammation in an individual patient is a determinant factor in the rate of growth and potency to (successfully) metastasize during surgical removal of the tumour. Furthermore, the grade of inflammation appears to have predictive

value in determining how successful anti-inflammatory treatment will be in reducing the inflammation, and consequently the outcome after the surgical procedure.
We eagerly await further study results focussing on this issue.

S-ketamine

S-ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist and is increasingly used to diminish opioid consumption and to reduce the risk of developing hyperalgesia and chronic pain (121-133). However, there is strong evidence that the use of S-ketamine results in a decrease of the number of NK-cells with an associated reduction of autonomic defence mechanisms. Furthermore, an evident correlation has been found between stimulation of the beta-adrenergic system and increased possibility of cancer recurrence and/or development of metastases (134-138). Strikingly, the tumour-enhancing effects of S-ketamine could largely be undone by administering beta-blockade.
This may suggest that stimulation of the beta-adrenergic system can have an unfavourable oncological effect, regardless of the type of underlying stimulating mechanism. Pain, surgical stress and administration of S-ketamine all result in stimulation of beta-adrenergic receptors. Should this hypothesis prove to be true, one could consider administering beta-blockade to surgical patients treated with S-ketamine, to neutralize it's potentially tumour promoting effects.

Apart from the surgical inflammatory stress response and the effects of different pharmaceuticals on the oncologic process, perioperative hypothermia and blood transfusions have also been mentioned as factors capable of influencing tumour evolution. Study results on these factors are not unambiguous either. Ben-Eliyahu et al found a correlation between perioperative hypothermia, reduced immunity and, as a result, tumour promotion (139). Yücel et al on the other hand were not able to confirm this correlation in their study. Therefore, they concluded that mild hypothermia does not affect tumour recurrence or mortality (140).
The same goes for receiving blood transfusions during surgery. In their study on prostate carcinoma, Ness and co-workers found no effect of blood transfusions on cancer recurrence (141). Amato on the other hand found evidence for some correlation in his Cochrane

Database Review (142), whilst Kekre's results show that duration of storage of red blood cells is of no influence on cancer recurrence or overall survival (143). However, in the latter study, multivariate analysis revealed that blood transfusion of more than 6 units was associated with higher cancer recurrence.
Finally, Yeoh and colleagues were also unable to detect any association between allogenic blood transfusion and systemic tumour progression and/or survival outcomes in their retrospective study on patients undergoing radical prostatectomy (144).
Based on the results of the randomized controlled FOCUS trial, Carson and co-workers report that liberal blood transfusion does not affect mortality compared with a restrictive transfusion strategy in a high-risk group of elderly patients with underlying cardiovascular disease or risk factor. In this study, elderly patients (> 50 years) with a history of or risk factors for cardiovascular disease, and with postoperative haemoglobin (Hb) concentrations < 100 gr/L within 3 days of surgery to repair a hip fracture, were randomly allocated to either liberal transfusion in which they received blood transfusion to maintain Hb level at 100 g/L (= 6,2 mmol/L) or higher. Or, restrictive transfusion in which they received blood transfusion when Hb level was lower than 80 g/L (= 5,0 mmol/L) or if they had symptoms of anaemia. Obviously, this study did not focus on cancer patients, but results indicate that a restrictive transfusion strategy doesn't affect mortality or cause of death per se in a high-risk group of elderly patients with underlying cardiovascular disease with a follow-up of 3 years (145).

As mentioned previously in the case of S-ketamine, there is growing evidence that stress and β-adrenergic stimulation may have an effect on tumour development and progression. Yand et al. state that chronic stress may contribute to gastric cancer progression by increasing the secretion of Interleukin-6 (IL-6). IL-6, as we know, is known to be elevated in individuals experiencing chronic stress and is also involved in oncogenesis and cancer progression (146).
Choi and colleagues claim that there is evidence that beta-blocker use can be associated with prolongd survival of cancer patients, especially patients with early-stage cancer treated primarily with surgery. This claim is based on a meta-analysis (147).

For a more comprehensive review of the impact of (adrenergic) stress on cancer we refer to the papers published by Meier and Eng (148-149).

In their review, Tang et al. expand further on the role of stress hormones, nicotine and β-adrenergic receptors on cancer cell proliferation, apoptosis, invasion and metastasis (150). Nagaraja and colleagues emphasize the importance of the knowledge of the β-adrenergic receptor status of tumour cells in choosing the best β-blocker for potential adjuvant therapy (151).

Rosenne and colleagues have studied the in vivo suppression of NK-cell cytotoxicity (NKCC) by stress and surgery. Their results indicate that both endogenous and exogenous elevated corticosterone levels can suppress in vivo NKCC levels, but only under some conditions, and mostly secondary to to the NK-suppressing effect of epinephrine. Specifically, corticosterone-induced NKCC suppression occurred (i) only under prolonged, but not short exposure to stress; (ii) was smaller than the prominent impact of epinephrine; (iii) was mostly ascribed to corticosterone-induced potentiation of the effects of epinephrine or/and prostaglandins; and (iv) was completely abolished through antagonizing epinephrine or/and prostaglandins (152).

1. Head, neck and throat malignancies

Airway management plays a key part in anaesthesia in surgical oncology of head, neck and throat malignancies. For more information on this topic, we refer to the numerous textbooks and training programs available. In our clinic, where a large number of our patients receive treatment for this type of cancer, the so-called awake flexible fiberoptic intubation (FFI) is used on a regular and important basis. In a patient with an expected difficult airway, flexible fiberoptic intubation remains the gold standard.

However, when a patient has an interdental gap of 3 cm or more, one can consider primarily ventilating the patient's lungs using an i-Gel size 4. Subsequently an endotracheal tube size 7.0 can be inserted through the i-Gel into the trachea, guided by a flexible scope located inside the tube. If one wishes so, the i-Gel can then be removed whilst the endotracheal tube is kept in its place using surgical forceps. Correct positioning of the endotracheal tube is easily achieved by using the flexible scope. This method is known as the "Srámek - Keijzer method" in our clinic (153) and is increasingly used in case of an unexpected difficult airway (154).

Apart from a potentially difficult airway, anaesthesia in the surgical treatment of head, throat and neck malignancies differs from other types of surgery, mainly because prolonged adjuvant neuraxial blockade is not readily feasible in this area of the body. Although cervical epidural anaesthesia is sometimes used in the treatment of (chronic) pain, its perioperative use isn't generally accepted.
One therefore depends on general anaesthesia combined with intravenous administration of analgesics. Opioids are the classic choice of medication. However, previous studies have shown that opioids have the potential to affect immunity and autonomous defence mechanisms unfavourably (48-58) and even to potentially increase cancer recurrence (53-58,155). In that view, one could advocate a perioperative strategy in which the consumption of opioids is reduced as much as possible without affecting the quality of analgesia. In other words, aiming at maximal reduction of the (surgical) inflammatory stress response with minimal impact on immunity and autonomous defence mechanisms.

Theoretically, opioid reduction can be achieved by alternatively using:

1. S-ketamine. NMDA receptor antagonist: known for its analgesic properties, reduced opioid consumption and hopefully a decrease in chronic pain and hyperalgesia (93-131,156).

2. Superficial cervical plexus blockade. Several studies have shown that superficial cervical plexus blockade leads to both improvement in pain management and reduction of opioid consumption (157-160). Based on previous study results, one could advocate the use of ropivacaine, rather than bupivacaine, because of its tumour inhibiting properties (44,45).

3. Co-medication with paracetamol and COX-2 inhibitors (77-79). Keeping in mind the diversity of diclofenac's working mechanism, this NSAID may be preferable to other NSAID's (161). However, it should be mentioned that based on recent findings the use of diclofenac in patients with cardiovascular disease may be contraindicated.

Unfortunately, only one study could be identified focussing on the effects of anaesthesia on cancer recurrence in malignancies of the head, neck and throat. In their retrospective (propensity-matched) study, Merquiol and colleagues report that combined epidural and general anaesthesia was associated with significantly increased cancer-free survival compared with general anaesthesia alone in laryngeal and hypopharyngeal cancer surgery (162).

Incidentally, Li and co-workers claim that continuous high thoracic epidural anaesthesia attenuates hippocampal apoptosis and behavioural deficit after global cerebral ischaemia, and that these protective effects are associated with the improved microcirculation and reduced oxidative stress (163). This claim is based on their study in which fifteen-minute global ischaemia was established by 4-vessel occlusion in adult rats. Bupivacaine 0,5% or saline 0,9% was infused continuously to the thoracic epidural space through the T4-5 intervertebral space from 15 minutes before ischaemia to 24 hours or 72 hours after

ischaemia. Both the hyperperfusion and hypoperfusion after reperfusion were improved by high thoracic epidural anaesthesia.

Seyedmajidi and colleagues report that a high level of cyclooxygenase -2 (COX-2) expression is found in oral squamous cell carcinoma and dysplasia compared to normal oral mucosa. Furthermore, a positive correlation is reported between COX-2 expression and severity of dysplasia (164).
Hsu et al. claim that epidermal growth factor-induced (EGF-) COX-2 expression enhances head and neck squamous cell carcinoma metastasis via activation of the fibronectin sihnalling pathway. The inhibition of COX-2 expression and activation may therefore be a potential strategy for the treatment of EGF-mediated head and neck squamous cell carcinoma metastasis (165).
This emphasizes the relationship between inflammation and oral squamous cell cancer.

Based on their retrospective study, Young et al. endorse the importance of the neutrophil-to-Lymphocyte ratio (NLR) as an independent prognostic factor in oropharyngeal carcinoma treated with chemoradiotherapy (109).
It has to be mentioned, however, that, according to Al and colleagues, NLR may be influenced by cigarette smoking. Based on their cross sectional study, they conclude that heavy smokers exhibit dyslipidemia with increased RBC count, total leucocyte count with specific increase in neutrophils (166).

Based on their nested case-control study, Macfarlane and co-workers claim that the use of NSAID's is associated with significantly reduced risk of upper aerodigestive tract (UADT) and oesophageal cancer. The use of aspirin, however, was associated with a non-significant risk of reduction of cancer of UADT, head and neck or the oesophagus (167).

Kum et al. even claim that NLR can be used to differentiate between laryngeal squamous cell carcinoma, benign laryngeal lesion and precancerous laryngeal lesion. This claim is based on their retrospective study involving 209 patients with laryngeal lesions. Patient files were reviewed for clinical, histopathological and laboratory data. According to the histopathological findings, these patients were divided into three groups: the benign

laryngeal lesion group (BLL), the precancerous laryngeous lesion group (PLL) and the laryngeal squamous cell carcinoma group (LSCC). The mean NLR's of the three groups were 2,12 ± 0,86 (BLL), 2,32 ± 0,68 (PLL) and 3,46 ± 1,51 (LSCC), respectively. This difference was statistically significant (168).

Huang and colleagues have studied the prognostic value of the pretreatment circulating neutrophil count (CNC), circulating monocyte count (CMC), and circulating lymphocyte count in human papillomavirus (HPV)-related (HPV+) and HPV-unrelated (HPV-) oropharyngeal carcinoma. Based on this cohort study they conclude that a high CNC and a high CMC independently predict inferior overall survival and recurrence-free survival, whereas a high CLC predicts better recurrence free survival and marginally better overall survival in HPV+ oropharyngeal cancer patients. This association was not apparent in HPV- patients (169).

Farhan-Alanie et al. state that the modified Glasgow Prognostic Score (mGPS) of activated systemic inflammation seems to be a powerful adverse prognostic indicator in resectable oral squamous cell carcinoma (170). The modified Glasgow Prognostic Score is calculated by measuring the serum levels of C-reactive protein and albumin. A serum C-reactive protein level ≤ 10 mg/l corresponds with a mGPS of 0; C-reactive protein > 10 and albumin ≥ 35 g/l corresponds with a score 1; C-reactive protein > 10 and albumin < 35 g/l corresponds with a mGPS 2 (171).
Selzer and colleagues confirm the importance of the GPS and modified GPS prognostic systems in primarily irradiated locally advanced head and neck cancer patients. A prognostic relevance was not found in patients irradiated postoperatively (172).

Xie et al. conclude that stress hormones may affect oral cancer behaviour by influencing the tumor microenvironment through circulating blood. This conclusion is based on the results of their study, in which the relationship between pre-surgical psychological problems, tumour histology, circulating blood catecholamines and glucocorticoid levels among oral cancer patients was investigated. In 75 patients, 40 patients with oral cancer and 35 patients with begign oral tumours, psychological problems were ascertained with Symptom Checklist-90-revised Inventory. Results showed that patients with oral cancer had higher

scores for symptoms of depression and obsessive-compulsion. Otherwise, there were no significant differences with respect to psychological problems between both groups. Mean concentrations of catecholamine and glucorticoid in peripheral blood in the oral cancer group were higher than those in the benign oral tumour group (173).

Majumdar and colleagues claim that preoperative intravenous injection of paracetamol results in superior pain management and earlier discharge from hospital in patients undergoing palliative head-neck surgery. The authors base this claim on the results of their prospective, double-blinded, and randomized study. In this study, 80 patients scheduled for palliative head-neck cancer surgery were randomly divided into two groups. Patients in group P received 1000 mg intravenous paracetamol 5 minutes before induction, patients in group F received intravenous placebo. For the rest, perioperative care was identical for both groups. Results revealed that mean visual analogue score (VAS) was lower in the first and second postoperative hours in the paracetamol group. Fentanyl requirement was less and the need for rescue analgesiac was delayed in the paracetamol group. Furthermore, patients in the paracetamol group had a shorter surgical intensive care and hospital stay compared with patients in the placebo group. The authors conclude that intravenous paracetamol is an effective preemptive analgesic after head-neck cancer surgery (174).

2. Intra-thoracic malignancies

2.1 Lung carcinoma

Several studies have been published focussing on intra-thoracic malignancies, and by far most of these studies deal with postoperative analgesia.

Thakur demonstrated the role of diclofenac as a chemo-preventive agent, exerting its effects by induction of apoptosis in certain types of cancer, like for instance lung carcinoma, and by inhibition of COX-2 (175).
Moody and colleagues report that S-diclofenac inhibits the growth of non-small cell lung cancer (NSCLC) and reduces prostaglandin E2 (PGE2) levels (176).
Nesher showed in his study that perioperative use of S-ketamine not only reduces opioid consumption but that it is also well tolerated in trans-thoracic surgery (156).

Mathews and Nesher state that in case epidural analgesia is contraindicated in a patient undergoing thoracotomy, the preferred treatment should be to add S-ketamine to morphine administered via a PCA-pump, in order to reduce opioid consumption and to obtain better analgesia, without any significant side effects (177,178).

Melamed and Shakhar however, showed that S-ketamine should not be classified as a panacea. Administering S-ketamine has been shown to induce stimulation of the beta-adrenergic system. This in turn induces suppression of NK-cell activity and therefore tumour enhancing effects, potentially stimulating the development of metastases (134,135). In the study, rats were injected with cancer cells and subsequently exposed to different types of anaesthetics. In rats that were exposed to S-ketamine and thiopental an increase of viable tumour cells was found in the lung during autopsy (by respectively factor 5.5 and 2). By contrast, this effect was not encountered in rats exposed to propofol or diazepam. Exposure to propofol and diazepam had no effect on the amount or activity of NK-cells either. This finding is in shrill contrast to exposure to S-ketamine and/or thiopental, which in both cases resulted in a significant decrease in number and activity of NK-cells.

Yoshioka et al demonstrated that thoracic epidural analgesia results in a decrease of opioid consumption and better analgesia in both trans-thoracic surgery and video-assisted-thoracoscopic surgery (VATS) (179). Oddly enough, Helms and colleagues found no reduction in morphine consumption (and/or better analgesia) after local anaesthetics were administered via a paravertebral catheter that had been inserted by the surgeon during thoracotomy. This finding strongly suggests the existence of a preemptive effect (180).
It is noteworthy that insertion of a paravertebral catheter according to the landmark technique can result in a high number of incorrect positioned catheters, up to 50% (181).

In an attempt to ameliorate postoperative pain following thoracotomy, Gebhardt et al., and Ried et al. have studied the effectivity of the ON-Q® local anaesthetic –infiltrating catheter. The ON-Q® Pain Relief System is a non-narcotic elastomeric pump, placed by the surgeon intraoperatively, that automatically and continuously delivers a regulated flow of local anesthetic to a patient's surgical site or in close proximity to nerves, providing targeted pain relief for up to five days (Halyard).
In their retrospective study, Gebhardt et al. have compared thoracic epidural analgesia with ON-Q infiltrating catheters in patients undergoing open thoracotomy. Results show that patients who received thoracic epidural analgesia had lower average pain scores on day 2 than did patients in the ON-Q group. Patients in the ON-Q group reported higher maximum pain scores on days 1 and 2, and at the time of discharge. However, patients in the ON-Q group were discharged an average of 1 day earlier. Therefore, the authors conclude that even though the maximum pain score was higher in the ON-Q group, patients were comfortable enough to be discharged earlier, resulting in cost savings (182).
Ried et al. also compared the ON-Q catheter system with thoracic epidural analgesia in patienst undergoing thoracotomy. Based on the results of their prospective, non-randomized trial the authors conclude that sufficient analgesia after thoracotomy can be achieved with the intercostal ON-Q system in patients, who cannot receive thoracic epidural analgesia (183).
Although cost-saving aspects certainly play an important role, insufficient control of the surgical inflammatory stress response might also prove more costly in the longer term.

Engelhardt and co-workers have conducted a retrospective study, in which epidural analgesia for pulmonary resections has been compared with subpleural analgesia, especially focussing on the morbidities associated with both analgesic techniques. In patients undergoing lobectomy for lung cancer through a thoracotomy or thoracoscopy, either an epidural or a subpleural catheter was placed. Patients in the subpleural catheter group were more likely to have undergone thoracoscopic surgery, and were more likely to develop intestinal complications compared with the epidural group. Meanwhile, patients in the epidural group were more likely to experience postoperative pruritus (morphine effect?), had longer intensive care unit stays, but were less likely to use a patient-controlled analgesia pump (184).

Jones suggests a greater pro-inflammatory response in patients undergoing lung resection via thoracotomy compared with VATS (185). This finding is in accordance with previous reports indicating that the level of tissue damage caused by a surgical intervention determines the level of immunosuppression (7).

Interestingly, Ju et al. have studied the effects of inhaled budesonide on ventilatory mechanics and the inflammatory response in patients undergoing one-lung ventilation for lobectomy. Based on the results of their prospective, double-blind study, they conclude that preoperative budesonide inhalation, compared with saline inhalation, reduced both peak and plateau ventilatory pressures. Furthermore, preoperative budesonide treatment also reduced the concentrations of tumour necrosis factor-α, interleukin-1β, interleukin-6 and interleukin-8 in bronchoalveolar lavage fluid, but increased interleukin-10 30 minutes after re-expansion (186).

As mentioned previously, Cata and colleagues report that, based on their retrospective survey, intraoperative opioid use is associated with decreased overall survival in stage I, but not in stage II or III non-small cell lung cancer (55).
Maher et al also suggest an association between increased doses of opioids during the initial 4-day postoperative period with a higher recurrence rate of non-small-cell lung cancer in their retrospective analysis (56).

Lennon et al, on their turn suggest a possible direct effect of Mu Opioid Receptor (MOR) stimulation on opioid and growth-factor-induced proliferation, migration and epithelial mesenchymal transition (EMT) in human lung cancer. In their study, morphine was shown to promote cell proliferation and invasion of human lung cancer cells (57).

Zylla and colleagues have examined retrospectively if long-term opioid requirement, independently of chronic pain, is assocoiated with reduced survival in patients with stage IIIB/IV non-small cell lung cancer (NSCLC). Based on the results of their study, they conclude that the severity of chronic cancer-related pain or greater opioid requirement is associated with shorter survival in advanced NSCLC, independently of known prognostic factors (187).

Piegeler demonstrates in his study that amide-linked local anaesthetics have the ability to inhibit migration of lung adenocarcinoma cells and inflammatory Src signalling, independent of sodium channel blockade (44).

As mentioned previously, evidence is growing that inflammation plays a key role in tumour development. Lately, several study results confirm that the preoperative neutrophil-to-lymphocyte ratio (NLR) offers important prognostic information on the aggressiveness of certain types of cancer. As demonstrated by Forget and colleagues, in patients with breast cancer and a high preoperative NLR (≥ 4), the use of NSAID's was associated with a reduction of the relative risk of cancer recurrence and mortality by more than 50%, compared to patients with a NLR < 4. In other words, breast cancer patients with a high NLR, a higher inflammatory grade, profited most of the anti-inflammatory treatment with diclofenac (92). The degree of inflammation, as reflected by the NLR, appears not only to correlate with the aggressiveness of cancer, but also with the effectiveness of treatment with anti-inflammatory drugs and/or chemotherapeutic agents.

Carus et al. conclude that a neutrophil index comprising elevated baseline neutrophils and absence of neutropenia was able to identify a high-risk group of non-small cell lung cancer (NSCLC) and ovarian cancer patients with only modest effect of chemotherapy (188). Interestingly, a high NLR in breast cancer patients was associated with a better response to

treatment with anti-inflammatory drugs. On the contrary, a high NLR in NSCLC and ovarian cancer patients is associated with less effect of chemotherapy. This difference could very well be explained by the fact that chemotherapeutic agents in general interfere far less profoundly with the inflammatory response than NSAID's. In fact, many chemotherapeutic agents are able to trigger and maintain inflammation.

The prognostic value of NLR, as a component of a newly validated prognostic score LENT (pleural fluid lactate dehydrogenase, Eastern Cooperative Oncology Group (ECOG) performance score, NLR and tumour type) is confirmed by Clive and co-workers. Based on their study results, they conclude that the LENT prognostic score predicts survival more accurately in patients with malignant pleural effusion than the ECOG prognostic score alone (189).

Cannon et al. state that pretreatment NLR and PLR (platelet-to-lymphocyte ratio) represent significant prognostic indicators of survival in patients treated for early-stage non-small cell lung carcinoma with stereotactic radiation (190).
On the other hand, Kang and colleagues claim that NLR, but not PLR, is associated with overall survival and progression-free survival in patients with small-cell lung cancer treated with platinum-based chemotherapy. In their retrospective study, a high NLR (≥ 4.0) at diagnosis was clearly associated with poor performance status, advanced stage, and lower response rate (191).
Zhang and co-workers confirm that a high NLR, but not PLR, is associated with worse overall survival in patients with non-small-cell lung cancer (192).
Based on their retrospective study, Lin et al. also conclude that high NLR (≥ 3.5) is an independent prognostic factor for worse progression-free and overall survival in epidermal growth factor recepror (EGFR)-mutated advanced non-small-cell lung cancer patients treated with first-line EGFR tyrosine kinase inhibitors (gefitinib or erlotinib) (193).

Miyazaki et al. have evaluated the prognostic significance of the Glasgow Prognostic Score (GPS) in surgically treated, over 80-years old patients with clinical stage I non-small-cell lung cancer (NSCLC). Based on the study results, the authors claim that the preoperative

GPS appears to be a useful predictor of overall survival and could be used as a simple prognostic tool in elderly patients with clinical stage I NSCLC (194).

Song and colleagues claim that total intravenous anaesthesia with propofol and remifentanil may reduce chronic post-thoracotomy pain syndrome (CPTS) at 3 and 6 months compared with inhalation anaesthesia with sevoflurane (195).

Finally, and as mentioned previously, the effects of β-adrenergic receptor stimulation on cancer development and/or progression attract growing attention. Schuller reports that data from recent experimental studies suggest that hyperactivity of the sympathetic branch of the autonomic nervous system, caused by chronic stress or chronic exposure to nicotinic agonists in cigarette smoke, contributes significantly to the development and progression of non-small cell lung cancer (196).

2.2 Mesothelioma

Study results focussing on mesothelioma and its relation to anaesthesia and/or anaesthesia techniques are scarce. We could identify only two studies addressing this issue.

Robinson and colleagues report that the use of NSAID's, COX-2 inhibitors or both have no effect on development or progression of mesothelioma in a human cohort exposed to asbestos. The authors confirmed this finding in a murine model.
An unexpected finding given the fact that asbestos has been shown to be able to cause chronic inflammation. One could therefore expect that NSAID's and COX-2 inhibitors would inhibit the development of asbestos-induced mesothelioma (197).

Linton and co-workers have investigated factors associated with survival in 910 patients with malignant pleural mesothelioma. Median overall survival was 10.0 months. Longer overall survival was associated with: age < 70 years, female gender, epithelioid subtype, ECOG status and Neutrophil-to-Lymphocyte ratio (< 5.0) (198).

3. Mamma carcinoma

Breast cancer is the most frequently encountered malignancy in women. In contrast to carcinoma of the prostate, the most frequently encountered malignancy in men, several studies have been published focussing on the relation between perioperative use of pharmaceuticals, anaesthetic technique and evolution of breast cancer.

Especially for this type of malignancy, strong evidence exists that surgery and surgical stress can lead to accelerated development of (micro) metastases (199). There are also indications that (in vitro) anti-inflammatory drugs, such as dexamethasone, restrain adhesion of breast cancer cells to endothelial cells. When properly administered, this might theoretically result in a decrease of metastases. Unfortunately this study did not state the (optimal dosage of dexamethasone to achieve this effect (200).
Gomez-Hernandez et al demonstrated that a dose of 8 mg of dexamethasone preoperatively results in less postoperative pain, nausea and vomiting in women undergoing mastectomy for breast cancer (201).

Bowers et al. report that daily use of a NSAID is associated with reduced oestrogen receptor α (ERα)-positive breast cancer recurrence in obese and overweight women. ERα-positive patients with an average body mass index of > 30 who used NSAID's on a daily basis had a 52% lower recurrence rate and a 28-month delay in time to recurrence. The mechanisms responsible are believed to be a greater macrophage cyclooxygenase (COX-2) expression and prostaglandin E2 (PGE2) production in obese patients (202).
The importance of COX-2 expression in predicting early relapse and aromatase inhibitor resistance in patients with ductal carcinoma in situ of the breast is supported by Generali and colleagues (203).
De Pedro and colleagues have performed a meta-analysis in which the effects of COX-2 inhibitors and other non-steroidal anti-inflammatory drugs on breast cancer risk were examined. Based on the results, they state that NSAID use reduces invasive breast cancer risk by 20% (204).
Allen et al. even claim that COX-2 is involved in the genesis of cerebrospinal fluid tumour cells in patients with breast cancer. Furthermore, the authors suggest that COX-2 inhibitors

should be investigated in patients with breast cancer with brain metastases for their ability to reduce cerebrospinal fluid tumour cell counts and prevent systemic recurrence (205).

As reported previously, Forget and colleagues claim that even a single intraoperative administration of a non-steroidal anti-inflammatory drug during breast cancer surgery, like for instance diclofenac, is able to reduce early cancer relapse 5-fold. This beneficial effect of treatment with NSAID's is reported more marked in patients with a higher Neutrophil-to-Lymphocyte ratio (NLR). The higher the NLR, the more profound the reduction in breast cancer relapse. In other words, the higher the degree of inflammation, the more successful treatment with non-steroidal anti-inflammatory drugs will be. Thus stressing the relationship between inflammation and (breast) cancer (92).
Nakano and colleagues indorse the importance of the NLR. Based on the results of their retrospective analysis they conclude that NLR is an independent prognostic factor for survival in Japanese women (110). A higher NLR is associated with worse outcome compared to a lower NLR. Interestingly, the authors also report that NLR was significantly higher in patients with lower body-mass index. A straightforward explanation for this finding can't be given.

Koh confirms that NLR is an independent prognostic factor for recurrence-free survival and overall-survival in breast cancer patients with oestrogen receptor/progesterone receptor (ER/PR)-positive and human epidermal growth factor receptor 2 (HER2)-negative subtype receiving neoadjuvant chemotherapy (206).
Dirican et al. corroborate the importance of NLR as a prognostic factor in breast cancer. In their retrospective study, NLR < 4.0 was clearly associated with longer disease-free and overall survival. Also the newly defined derived NLR (dNLR: neutrophil/leukocyte-lymphocyte ratio) proved prognostic for disease-free and overall survival (207).
Based on their observational study, Yao and co-workers conclude that preoperative NLR (and red cell distribution width-RDW) is a convenient, easily measured prognostic indicator for patients with breast cancer, especially in patients with the triple-negative subtype (208). In this study, patients with high NLR (> 2,57) showed a significantly lower overall survival rate than those with lower NLR (≤ 2,57).

Ozyalvacli et al. have studied preoperative NLR values in patients with primary breast carcinoma and benign proliferative breast disease. Based on the results, the authors conclude that preoperative high NLR (> 2,96) is a significant diagnostic predictor of distinction of breast cancer from benign proliferative breast disease. Furthermore, an elevated NLR is also an important prognostic marker for primary invasive breast cancer (209).

Cihan and colleagues, on the other hand, were not able to find any association between NLR and survival in patients with non-metastatic breast cancer who received adjuvant radio- and chemotherapy (210).

Recent study results published by Barron et al. demonstrate that women with breast cancer and prediagnostic aspirin use (COX1/COX2 inhibitors) were significantly less likely to present with a lymph node-positive tumour than patients who did not use aspirin. Furthermore, prediagnostic aspirin use was also associated with lower 5-year breast cancer-specific mortality among women with lymph node-negative tumours, but not node-positive tumours. However, there was no association between postdiagnostic aspirin use and breast cancer-specific mortality. Based on this nationwide population-based cohort study, the authors conclude that recent prediagnostic aspirin use (< 1 year) is protective against lymph node-positive breast cancer (211).

Allott and colleagues report that increased duration and regularity of NSAID use is associated with reduced breast cancer-specific mortality in women with estrogen receptor-positive cancer. There was no association for estrogen receptor-negative patients. The authors conclude that, if confirmed, these findings support the hypothesis that potential chemopreventive properties of NSAID's are mediated (partly) through suppression of estrogen biosynthesis (212).
In addition to this, Deb and co-workers report that a specific, newly synthesized naproxen derivative has even more powerful anti-inflammatory and anti-tumour properties than the parent compound naproxen sodium. The anti-tumour properties consist of induction of apoptosis in breast cancer cells and delay in the migration of cancer cells (213).

Finally, Cui et al. claim that regular use of NDAID's is inversely associated with breast cancer, particularly among overweight women. Therefore, they conclude that overweight women may benefit (even) more from the protective effects of NSAID's use than normal-weight women (214). This claim is based on their population-based, case-control study involving over 5000 women, in which regular use of any NSAID was associated with significantly reduced breast cancer risk.

In their study on mamma carcinoma, Gupta et al showed that morphine has the ability to promote tumour proliferation (15). Forget and co-workers studied the relationship between perioperative use of analgesics and cancer recurrence. They conclude that in their study only the use of NSAID's reduced probability of cancer recurrence. Other analgesics such as opioids and S-ketamine did not influence cancer recurrence in patients undergoing mastectomy (215). Legeby and colleagues demonstrate in their study that the use of diclofenac during mastectomy may result in increased blood loss due to its effects on coagulation (216).
Wen et al. report that combining the non-steroidal anti-inflammatory drug flurbiprofen with the opioid fentanyl results in a decrease in serum concentrations of vascular endothelial growth factor-C, tumour necrosis factor-α and interleukin-1β. Since all of these have been associated with the recurrence and metastasis of breast cancer after surgery, one could therefore conclude that the addition of flurbiprofen to fentanyl has the potential to diminish breast cancer recurrence and metastasis (217).

Several studies have demonstrated that loco-regional analgesia, such as paravertebral blockade, results in more effective pain control and also in less adverse effects (33,218-222). Along this line, the study performed by Albi-Feldzer and colleagues is worth mentioning. Local wound infiltration with ropivacaine was shown to result in a distinct reduction of postoperative pain albeit without any effects on chronic postoperative pain (patients being followed for 12 months postoperatively) (223). One study reported indications of a lower surgical stress response with significantly lower levels of Cortisol, C-reactive protein and blood glucose when paravertebral analgesia was administered. However, an effect on angiogenic factors could not be demonstrated (224). Looney et al, on the other hand, showed that different anaesthetic techniques used in breast cancer surgery do

have an effect on angiogenesis by influencing serum concentrations of angiogenesis related factors (225).
Sultan reports that cytokine response is attenuated following breast cancer surgery when general anaesthesia is replaced by paravertebral blockade, as expressed by altered serum levels of interleukin (IL)-6, IL-10, IL-12 and interferon-gamma (IF-γ) (226).
Compagnone and co-workers underline the value of paravertebral blockade in older patients undergoing elective mastectomy in one-day surgery (227).

Two studies revealed that the use of local anaesthetics, in either paravertebral of epidural blockade, may result in a lower probability of developing chronic pain (228,229). Shin and Cho demonstrated in their study that remifentanil associated hyperalgesia could be induced by combining sevoflurane anaesthesia with high doses of remifentanil during breast cancer surgery. This effect, however, was not encountered when propofol anaesthesia was combined with remifentanil (230).
Cho and co-workers state in their study that intravenous propofol anaesthesia is associated with a lower incidence of chronic pain after breast cancer surgery than sevoflurane anaesthesia (231).

Aufforth, in his study, puts forward a possible role for paravertebral blockade in patients undergoing mastectomy with immediate breast reconstruction using tissue expanders. Paravertebral blockades would result in better pain management and a decrease in opioid consumption (232). According to Exadaktylos, the probability of cancer recurrence or metastases is reduced by a factor 4 when paravertebral blockades are used instead of intravenous opioids in breast cancer surgery (233). Deegan demonstrates in his paper that propofol anaesthesia combined with paravertebral blockade decreases proliferation of the cancer cell more than cell migration when compared to sevoflurane/opioid anaesthesia (234).
As mentioned previously, Jaura has shown that sevoflurane anaesthesia combined with opioid analgesia for primary breast cancer surgery reduces apoptosis in oestrogen receptor (ER)-negative breast cancer cells to a greater extent than propofol anaesthesia combined with paravertebral analgesia (33).

Buckley and colleagues have investigated the effect of serum from women undergoing primary breast cancer surgery on healthy human dodor natural killer cell function and cytotoxicity against oestrogen and progesterone receptor-positive breast cancer cells. In this randomized prospective trial, patients were randomized to propofol-paravertebral block (PPA) or sevoflurane-opioid (GA) anaesthetic technique. Donated serum (before surgery and 24 hours after surgery) was cultured and examined. The authors conclude that serum from women with breast cancer undergoing surgical excision who were randomized to receive a PPA anaesthetic technique led to greater human donor NK-cell cytotoxicity in vitro compared with serum from women who received GA. This conclusion is based on the finding that serum from PPA subjects did not alter normal NK marker expression or secretion of cytokines. Serum from GA subjects, on the other hand, reduced NK-cell activating receptor, interleukin-10 (IL-10), and interleukin-1β (IL-1β). Furthermore, an increase in NK-cell and apoptosis was observed with PPA serum, but not GA serum, treated cells (235).

Naja and co-workers report that the addition of clonidine to the local anaesthetic in paravertebral blockades enhances the analgesic effects of the blockade with a further reduction of opioid consumption (236).

Mohamed et al. state that the addition of dexmedetomidine (1 μg/kg) to bupivacaine 0.25% (20 ml) in thoracic paravertebral blockade in patients undergoing modified radical mastectomy improves the quality and the duration of analgesia and also provides an analgesic sparing effect with no serious side effects (237).

Goravanchi and colleagues confirm that the addition of epinephrine, clonidine, and dexamethasone to ropivacaine in multiple-injection, one-time paravertebral block in patients undergoing breast cancer surgery prolongs the clinical duration considerably. Ropivacaine as a sole agent in paravertebral blockade is reported to have a clinical duration of up to 6 hours (238).

Coopey et al. claim that the use of preoperative paravertebral blockade decreases length of stay in patients undergoing mastectomy followed by immediate reconstruction (239).

Arunakul and Ruksa, on their turn, claim that single-injection paravertebral blockade can reduce postoperative opioid requirement, pain, and severity of nausea and vomiting in patients undergoing modified radical mastectomy (240).
Gu and colleagues also have studied the effects of paravertebral blockade in patients undergoing breast cancer surgery. In their prospective randomized study, patients undergoing breast cancer surgery were randomly assigned to either paravertebral blockade analgesia and propofol general anaesthesia (PPA), or sevoflurane general anaesthesia with opioid analgesia (SOA). Both groups were compared for opioid consumption and pain outcomes. Results showed that both pain scores and opioid consumption were significantly lower in the paravertebral-propofol group compared to the sevoflurane-opioid group (241).

Finally, Karmakar reports that the incidence of chronic pain at 3 and 6 months after modified radical mastectomy (MRM) is not affected when thoracic paravertebral blockade is used in conjunction with general anaesthesia compared with general anaesthesia and opioids. Nonetheless, patients who receive thoracic paravertebral blockade (TPVB) report less severe chronic pain, exhibit fewer symptoms and signs of chronic pain, and also experience better physical and mental health-related quality of life. These conclusions are based on the results of a prospective study in which patients undergoing MRM were randomized into 3 groups: Group 1: standardized general anaesthesia (GA); Group 2: GA with a single-injection TPVB and placebo paravertebral infusion; Group 3: GA with a continuous TPVB (242).

Bouman and colleagues have compared paravertebral blockade with local wound infiltration in patients undergoing unilateral major breast surgery under general anaesthesia. In a randomized controlled trial, 46 patients undergoing unilateral major breast surgery in a day-care or short-stay setting were studied. Surgery was performed under general anaesthesia with either paravertebral blockade or local wound infiltration. Surgical procedures included wide local excision, mastectomy and modified radical mastectomy. Sentinel node procedure, axillary dissection, or immediate prosthetic breast reconstruction was reported mandatory in case of wide local excision and optional in case of mastectomy or modified radical mastectomy.

No significant difference in visual analogue scale (VAS) pain score was noted 24 hours after surgery or at any point postoperatively until postoperative day 2. Therefore, the authors conclude that local wound infiltration and paravertebral blockade are equally effective in the treatment of acute postoperative pain after major oncological breast surgery. Since local wound infiltration is easily to perform with fewer complications and it is more cost-effective it should be preferred over paravertebral blockade (243).
However, it has to be mentioned that only 19% (46) of the eligible patients gave informed consent. Therefore, selection bias can't be ruled out. Furthermore, it remains unclear whether or not surgical procedures were equally distributed between the two groups. For instance, it may be obvious that a mastectomy followed by latissimus dorsi myocutaneous flap reconstruction results in more extensive tissue damage and therefore in a more extensive inflammatory stress response compared to a wide local excision.

Chiu et al. also have studied the effects of paravertebral blockade (versus local anaesthetic infiltration) on persistent postoperative pain in patients undergoing breast cancer surgery. In this prospective and randomized study persistent postoperative pain (PPP) was defined as an NRS value > 3 at rest or with movement 1 year following surgery. Of the included 145 patients, only 9 patients (8%) met criteria for PPP 1 year following surgery: 5 patients were treated with PVB, and the remaining 4 with local anaesthetic infiltration, in combination with general anaesthesia. The authors conclude that the incidence of chronic pain 1 year following major breast cancer surgery was low, but that it had a large impact on the affected patient's arm mobility and quality of life (244).

As discussed previously, local anaesthetics, like ropivacaine and lidocaine, appear to inhibit proliferation as well as growth of cancer cells in vitro. Piegeler demonstrated that only local anaesthetics of the amide type display these inhibiting properties, in contrast to local anaesthetics of the ester type (44). Lirk and colleagues, on their turn, report that lidocaine and ropivacaine, but not bupivacaine, demethylates deoxyribonucleic acid in breast cancer cells in vitro, thus reactivating tumour suppressor genes and inhibiting tumour growth (45). Votta-Velis and co-workers demonstrate that amide-linked local anaesthetics attenuate tumour cell migration and signalling pathways enhancing tumour growth and metastasis (47).

In this connection, it is noteworthy that propofol conjugates such as propofol-docosahexaenoate and propofol-eicosapentaeonoate have been (and still are being) studied as possible agents in the treatment of breast cancer. This interest is based on their ability to inhibit both cell adhesion and migration, and induction of apoptosis in breast cancer cells (245). These findings are in shrill contrast to earlier study results that ascribed unfavourable properties to propofol in relation to the progression of cancer (19).

Recently two new techniques have been described for pain management in major breast surgery: the paravertebral lamina technique and the pectoral nerves I, and II blocks (246,247). Until now, no study results have been published regarding the effectiveness of the paravertebral lamina technique in relation to breast cancer. With respect to the pectoral nerves I, and II blocks, Bashandy and Abbas claim that the combined Pecs I, and II block is a simple, easy-to-learn technique that produces good analgesia for radical beast surgery (247).

Kulkarni et al. report that cervical epidural anaesthesia is a well-established technique for surgery of the neck, chest and upper arms. In their prospective double-blind study, the authors have investigated the safety of cervical epidural analgesia and compared the efficacy of 0,25% bupivacaine with 0,375% ropivacaine in patients undergoing radical mastectomy. There were no significant differences reported in the onset of sensory block in both groups. The mean motor blockade score, defined as time to achieve complete blockade and time to grade I motor recovery, was significantly longer in the bupivacaine group. However, respiratory distress developed in two of the 20 patients that were treated with bupivacaine, requiring general anaesthesia with endotracheal intubation. Therefore, the authors conclude that 0,375% ropivacaine is safer than 0,25% bupivacaine for cervical epidural analgesia for radical mastectomy (248).
It has to be mentioned that, in our hospital, cervical epidural anaesthesia is not used in the operating theatre.

Bharti and colleagues claim that preoperative administration of gabapentin reduces intraoperative propofol requirements and postoperative analgesic consumption in breast

cancer patients undergoing total mastectomy. This claim is based on the results of their prospective, randomized double blind study in which the effects of administration of gabapentin (600 mg two hours prior to surgery) on propofol consumption, hemodynamic variables, and postoperative pain relief in breast cancer surgery were studied (249).

Lately, treatment with intravenous lidocaine during and after surgery also attracts attention. Grigoras and co-workers showed that perioperative intravenous administration of lidocaine in breast cancer surgery resulted in a decrease of persisting postoperative pain for up to 3 months after surgery. Strangely enough, no difference could be found in the consumption of analgesics for both the group with and without intravenous lidocaine (250). Until now, no other study results could be identified focussing on the effects of intravenous lidocaine on cancer growth and/or recurrence in patients with breast cancer.

Interestingly, and as mentioned previously in the case of S-ketamine, stimulation of the beta-adrenergic system may have unfavourable oncological effects. Studies have shown that pain and surgical (inflammatory) stress can affect the autonomic defence mechanisms in a negative way. In addition, an evident correlation has been reported between stimulation of the beta-adrenergic system and increased chance of developing metastases (135-139). The aforementioned findings suggest that stimulation of the beta-adrenergic system can thus have an unfavourable oncological effect, regardless of the type of underlying stimulating mechanism. Stimulation of beta-receptors, either by pain, surgical inflammatory stress and/or pharmacologically induced beta-adrenergic stimulation may thus result in promotion of the tumour. This hypothesis is supported by the papers published by Botteri and De Giorgi (136,137). In both studies, the use of beta-blockers was associated with a significantly decreased risk of respectively breast cancer-and melanoma-related recurrence, metastasis and death.

Iseri et al. have investigated the efficacy of propranolol, atenolol, and an experimental non-selective β-adrenergic receptor antagonist (ICI118,551) on proliferation, migration, and invasion of non-stimulated breast, colon, and hepatocellular cancer cells. The results indicate that the effects on proliferation, migration, and invasion are both β-adrenergic receptor antagonist, and dose-dependent (251).

Mahdian and co-workers claim that cell viability is decreased in both breast cancer, and cervical cancer cells by phosphodiesterase inhibitors and beta-adrenergic receptor agonists (252).

However, Cardwell and colleagues have conducted a nested case-control study in which the association between breast cancer-specific death and beta-blocker usage was studied. The authors report that no significant association could be found between post-diagnostic beta-blocker usage, breast cancer-specific mortality and breast cancer progression (253).

Strikingly, Gargiulo et al. have demonstrated that the endogenous adrenergic receptor agonist epinephrine causes opposite effects in non-tumourigenic and tumour cells. In non-tumour breast cells, epinephrine decreased cell proliferation and migration, as well as cell adhesion. Therefore, the authors conclude that differential β2-adrenergic receptor expression defines the phenotype of non-tumorigenic and malignant human breast cell lines (254).

Previous experimental studies in mouse models have shown that chronic stress can enhance breast cancer progression by increasing catecholamine levels and subsequent signalling of β-adrenergic receptors. Since catecholamines also signal α-adrenergic receptors, this type of signalling has also been studied in relation to cancer progression. Results show that increased α-adrenergic signalling is able to promote breast cancer growth too. However, since pre-synaptic α_2-adrenergic receptors suppress the release of norepinephrine by negative feedback, antagonism of α-adrenergic receptors can result in elevated catecholamines levels, which may increase β-adrenergic signalling.
Given these findings, Lamkin and co-workers have examined the effect of α-adrenergic blockade on breast cancer progression under non-stress and chronic restraint stress conditions in an orthotopic mouse model. Results revealed that chronic restraint stress increases primary tumour growth and metastasis to distant tissues (as expected), and non-selective α-adrenergic blockade by phentolamine significantly inhibits those effects. However, under non-stress conditions, phentolamine increases primary tumour size and distant metastasis.

Sympatho-neural gene expression for catecholamine biosynthesis enzymes was elevated by phentolamine under non-stress conditions, and the non-selective β-blocker propranolol inhibited the effect of phentolamine on breast cancer progression. Selective α_2-adrenergic blockade by efaroxan also increased primary tumour size and distant metastasis under non-stress conditions, but selective α_1- adrenergic blockade by prazosin did not.
The authors therefore conclude that these results are consistent with the hypothesis that α_2-adrenergic signalling can act through an autoreceptor mechanism to inhibit adrenergic catecholamine release, and, thus, modulate established effects of β-adrenergic signalling on tumour-relevant biology (255).

In their review, Obeid and Conzen expand further on the role of adrenergic signalling in breast cancer biology (256).

In the light of the foregoing, one could consider administering beta-blockers to surgical patients undergoing oncological surgery, in order to neutralize these potentially tumour promoting effects.

Although there is evidence that perioperative intravenous lidocaine administration might reduce the requirement of opioids, improve bowel function in abdominal surgery and shorten the length of hospital stay, Terwaki and colleagues were unable to confirm these findings for breast cancer surgery. Based on their double-blind, placebo-controlled randomized trial, the authors report that intravenous lidocaine during breast cancer surgery had no effect on opioid consumption, pain score, postopeartive nausea and vomiting (PONV), fatigue and or duration of postoperative hospital stay (257).

However, it has to be noted that previous studies has shown that amide-linked local anaesthetics display anti-tumour effects (40-45, 326). As mentioned previously, Lirk et al. report that lidocaine and ropivacaine demethylate deoxyribonucleic acid in breast cancer cells in vitro. This in turn reactivates tumour suppressor genes and inhibits tumour growth (45).
Li et al. have studied these effects and conclude that lidocaine demethylates DNA in breast cancer cells, and by doing so sensitizes the cytotoxicity of cisplatin (258).

4. Digestive tract malignancies

4.1 Oesophageal cancer
4.2 Gastric/ Biliary tract/ Hepatic/Pancreatic cancer
4.3 Small intestine cancer
4.4 Colorectal cancer

4.1 With respect to oesophageal malignancies, we could identify the following studies. Two studies focussed on the relationship between the occurrence of postoperative anastomotic leakage and perioperative presence of thoracic epidural analgesia. Michelet et al. demonstrated that the use of perioperative thoracic epidural analgesia in oesophageal resections is associated with a decrease in anastomotic leakage. This is believed to be the result of improved vascularisation of the anastomosis (259). Lai and co-workers were also unable to demonstrate any deleterious effect of thoracic epidural analgesia on anastomotic leakage in anterior resections. They did, however, find an evident reduction in length of hospital stay in case epidural analgesia was administered (260).

Xu and colleagues show in their study that the use of the intravenous anaesthetic propofol results in suppression of proliferation, invasion and angiogenesis in oesophageal squamous cell carcinoma cells (261). Hiller, in his database analysis involving 140 patients with a minimum follow-up of 2 years, also reports an association between effective postoperative epidural analgesia and medium-term benefit on cancer recurrence and survival following oesophageal surgery (262).

Heinrich et al. report that the results of their study underline the well-known clinical benefits of epidural analgesia for oesophageal surgery, including less opioid consumption and shorter duration of ICU hospitalization. However, the authors report to have found no evidence that further oncological outcome is determined or significantly influenced by the presence or absence of epidural analgesia (263). This retrospective analysis included 153 patients, of whom 118 patients received epidural analgesia. Epidural analgesia was avoided in 35 patients for reasons not mentioned.

Fares and colleagues have studied the effect of thoracic epidural analgesia on pro-inflammatory cytokines in patients subjected to protective lung ventilation during Ivor Lewis oesophagectomy. In their randomized controlled study, 30 patients were randomly allocated into 2 groups. Patients in the first group received general anaesthesia and were mechanically ventilated with 9 ml/kg during 2 lung ventilation, reduced to 5 ml/kg and 5 cm H2O positive end expiratory pressure (PEEP) during one lung ventilation. Patients in the second group received thoracic epidural analgesia and the same general analgesia and mechanical ventilation used in the first group of patients. Results showd that there was a significant reduction in mean arterial blood pressure and pulse rate in the second group during the intraoperative period and postoperatively. Mean resting and dynamic VAS scores were significantly reduced in the epidural group over all 3 postoperative days in comparison to the first group, as was the daily PCA morphine consumption. Blood levels of Interleukin-6 and Interleukin-8 were also significantly reduced in the epidural group over the entire study period. The duration of stay in the ICU was significantly decreased in the epidural group compared with the first group. There were no significant differences in post-operative adverse events between the two groups. Based on these results, the authors conclude that thoracic epidural analgesia reduced the systemic pro-inflammatory response and provided optimal post-operative pain relief. Although there were no significant differences in adverse events, there was a trend towards improved outcome (264).

Gu et al. support the conclusion that thoracic epidural analgesia (TEA) reduces the pro-inflammatory response and minimizes immune dysfunction. In their prospective and randomized study, patients undergoing thoracic surgery for oesophageal cancer were allocated into one of 4 groups. During surgery, patients in groups I en II received total intravenous general anaesthesia (TIVA), whereas patients in groups III and IV received combined TEA and TIVA. Postoperatively, groups I and III received postoperative patient-controlled intravenous analgesia (PCIA), whilst patients in groups II and IV received PCEA. Levels of cortisol and cytolines were measured in peripheral blood samples collected prior to anaesthesia and and different intervals after incision. Plasma levels of cortisol and cytokines increased significantly at the beginning of the operation in all groups, apart from group IV. In this group, no significant alteration in cortisol and cytokines levels was detected (265).

Zhang et al. have studied the safety and efficacy of a single-dose and bilateral ultrasound-guided-paravertebral blockade in patients undergoing combined thoracoscopic-laparoscopic oesophagectomy (TLE) along with intravenous sufentanil analgesia in combination with general anaesthesia. In this prospective study, 52 patients undergoing TLE were randomized into either the paravertebral or the control group. Patients in the paravertebral group were injected 3 times 10 ml of 0.5% ropivacaine at the right T5 and bilateral T8. Patients in the control group received saline injections of 10 ml at each site. After induction of anaesthesia, all patients received intravenous sufentanil analgesia.
Results revealed lower intraoperative mean sufentanil usage, and end-tidal sevoflurane concentrations in the paravertebral group. Postoperative pain scores, both at rest and on coughing, were also lower during the first 8 hours in the paravertebral (PVB) group. Cumulative sufentanil consumption, as delivered by patient-controlled analgesia, was also significantly lower in the PVB group at all time points. Furthermore, postoperative pulmonary function was better at the third postoperative day in the PVB group, with quicker hospital discharge and lower hospital costs, compared with the control group (266).

As mentioned previously, Macfarlane and co-workers claim that the use of NSAID's is associated with significantly reduced risk of upper aerodigestive tract (UADT) and oesophageal cancer. In this nested case-control study, the use of aspirin, in contrast to the use of NSAID's, was not associated with a reduced risk of oesophageal cancer (167).

Based on their meta-analysis, Paramanathan et al. claim that a high NLR (> 5.0) is associated with poorer outcome in patients undergoing surgery for oesophageal cancer (105).
These findings are confirmed by Yuan and colleagues. In their retrospective study involving patients with adenocarcinoma of the oesophagogastric junction undergoing curative resections, elevated preoperative NLR (≥ 5.0) was clearly associated with poorer disease-free and overall survival (DFS and OS). Interestingly, the platelet-to-lymphocyte ratio (PLR) did not significantly predict DFS or OS (267).

Yoo et al. have studied the association between NLR and survival after chemoradiotherapy for locally advanced oesophageal cancer. In their study, low pretreatment NLR (< 2.0) was clearly associated with longer progression-free and overall survival compared with the high NLR (≥ 2.0) group (268).

Li and co-workers confirm the prognostic significance of prechemotherapy NLR in patients undergoing radical oesophagectomy for locally advanced oesophageal squamous cell cancer. Their study results show that a prechemotherapy NLR > 5.0 was significantly associated with worse overall survival. Furthermore, NLR proved to be a superior prognostic predictor than platelet-to-lymphocyte ratio (PLR) (269).

Feng and colleagues have studied the usefulness of a new inflammation index for patients with oesophageal squamous cell carcinoma. A total of 293 patients who had undergone oesophagectomy were included and the inflammation index was calculated. This so-called advanced lung cancer inflammation index (ALI) was calculated as body mass index × serum albumin/NLR. Patients were then divided into two groups: ALI < 18 and ALI ≥ 18. Results showed that ALI was significantly higher in patients with large tumours, poor differentiation, deep invasion, and nodal metastasis. Furthermore, ALI proved to be a significant predictive factor of cancer-specific survival (270).

By contrast, Xie et al. state that preoperative PLR is significantly correlated with prognosis in patients undergoing surgery for oesophageal squamous cell cancer, but not NLR. In this study, the optimal cut-off value of preoperative PLR and NLR were 103.0 and 2.1, respectively (271).

4.2 Gastric/ Biliary tract/ Hepatic/Pancreatic cancer

In their study on pancreatic carcinoma, Mayorek and colleagues were able to demonstrate that diclofenac exhibits distinct anti-tumour activity (86). A finding previously encountered in the case of breast cancer and lung cancer.

Yon and co-workers demonstrate in their prospective, randomized, double-blind and placebo-controlled study, involving 36 patients undergoing subtotal gastrectomy, that pre- and intraoperative intravenous infusion with lidocaine reduces pain and opioid consumption without reported side-effects (272). However, VAS pain scores and administration of patient-controlled-analgesia (PCA) were significantly lower in the lidocaine group until 24 hours after surgery, and opioid consumption was significantly lower in this group until 12 hours postoperatively compared with the placebo group. Furthermore, no significant differences were detected in terms of nausea and vomiting, return to regular diet, length of hospital stay and patient satisfaction.

Kang cum suis report comparable results showing that intraoperative intravenous lidocaine reduces opioid consumption and hospital length of stay following open gastrectomy for stomach cancer in men (273).

Interestingly, Kim and colleagues point out that the short acting beta-blocker esmolol may play an immunomodulatory role in patients undergoing laparoscopic gastrectomy due to gastric cancer. In their prospective study 29 patients were enrolled, half of them was treated with esmolol during surgery and the remainder was treated with saline. Cytokines were quantified by sandwich enzyme-linked immunoassays before, during and after surgery. The esmolol group was associated with higher ratios of interferon-γ/interleukin-4 than the saline group. Furthermore, the postoperative increase in interleukin-6 was attenuated in the esmolol group, and the C-reactive protein level on the first postoperative day appeared significantly lower (274).

Liao et al. have studied the effects of the β-blocker propranolol on human gastric adenocarcinoma cell lines and report that propranolol inhibits both cell proliferation and

growth in a concentration-dependent manner. In addition, propranolol was also reported to induce apoptosis (275).
Meng and colleagues claim that the combination of the selective cyclooxygenase-2 inhibitor (COX-2) Celecoxib with chemotherapy drugs produces a synergistic antitumour effect, possibly by inhibiting the proliferation of gastric tumour cells and promoting apoptosis (276).

As mentioned previously, Zhang et al. have demonstrated that propofol exhibits anti-tumour effects by inhibiting growth of human hepatocellular cancer cells (22).

Iseri et al. have investigated the efficacy of propranolol, atenolol, and an experimental non-selective β-adrenergic receptor antagonist (ICI118,551) on proliferation, migration, and invasion of non-stimulated breast, colon, and hepatocellular cancer cells. Their results indicate that the effects on proliferation, migration, and invasion are both β-adrenergic receptor antagonist, and dose-dependent (251).

Li and colleagues claim that expression of monoamine oxidase A (MAOA), a catecholamine neurotransmitter degrading enzyme, is closely related to cancer vasoinvasion, metastasis, and poor prognosis in vitro and in vivo hepatocellular cancer models. In their study, MAOA suppressed norepinephrine/epinephrine-induced hepatocellular carcinoma invasion. These effects were primarily mediated through alpha-1A and beta-2 adrenergic receptors (277).

These findings fit in with previous results suggesting that stimulation of the beta-adrenergic system on its own may have unfavourable oncological effects. Previous studies have shown that pain and surgical stress can affect the autonomic defence mechanisms in a negative way. Furthermore there is also strong evidence that the use of S-ketamine results in a decrease of the number of NK-cells with a further reduction of autonomic defence mechanisms. In addition, an evident correlation has been reported between stimulation of the beta-adrenergic system and increased chance of developing metastases (135-139). Strikingly, the tumour-enhancing effects of S-ketamine could largely be undone by administering beta-blockade.

Kim-Fuchs et al. report that, based on their study in mice, neural β-adrenergic signalling appears to regulate pancreatic cancer progression, and suggest β-blockade as a novel strategy to complement existing tehrapies for pancreatic cancer. This suggestion is based on the finding that pharmacological activation of β-adrenergic signalling induced similar effects to chronic stress, and pharmacological β-blockade reversed the effects of chronic stress on pancreatic cancer progression (278).

In their review, Hefner et al. expand further on the role of stress, β-adrenergic signalling and pancreatic carcinoma (279).
Incidentally, Chisholm and colleagues have studied the β-adrenergic receptor expression in vascular tumours, and they conclude that β-blockade could potentially affect apoptosis and decrease responsiveness to vascular endothelial growth factor (280).

As discussed previously in the case of lung cancer, epithelial-mesenchymal transition (EMT) is a crucial event responsible for cancer cell invasion and metastasis (57).
Shan et al. claim that norepinephrine does not only induce EMT alterations in the morphological characteristics of gastric adenocarcinoma cells, but also increases the markers of EMT (281).

The aforementioned findings suggest that stimulation of the beta-adrenergic system can have an unfavourable oncological effect, regardless of the type of underlying stimulating mechanism. Stimulation of beta-receptors, either by pain, surgical inflammatory stress and/or pharmacologically induced beta-adrenergic stimulation may thus result in promotion of the tumour.

Lee and co-workers have compared the efficacy of intrathecal morphine combined with intravenous analgesia with thoracic epidural analgesia after conventional open gastrectomy. In this study, patients were randomly allocated into the intrathecal morphine combined with intravenous patient-controlled analgesia (IT) group or patient-controlled thoracic epidural (EP) group. In the IT group, patients were treated preoperatively with 0,3 mg of morphine intrathecally and received intravenous patient controlled analgesia (IVPCA) postoperatively. In the EP group, a thoracic epidural catheter was introduced and patients

were treated accordingly. Results revealed lower pains scores, less fentanyl consumption, a shorter time to ambulate and lower incidences of complications (postoperative ileus and pulmonary complications) in the EP group compared with the IT group. Therefore, the authors conclude that intrathecal morphine combined with intravenous analgesia is not as effective as patient-controlled thoracic epidural analgesia (282).

In contrast to other studies, Zhang et al. found that perioperative use of propofol resulted in an (dose dependent) increase in proliferation as well as invasive properties of gallbladder cancer cells. A good explanation for this finding cannot readily be given (19).

Interestingly, Cao and colleagues report in their recently published paper that postoperative epidural analgesia with morphine is associated with increased cancer recurrence and death, compared with postoperative intravenous analgesia with fentanyl in patients undergoing resection of hepatocellular carcinoma (283). These findings are in conflict with previous findings suggesting that epidural analgesia is associated with decreased cancer recurrence and better outcome. In this retrospective cohort study patients undergoing hepatic resection for hepatocellular carcinoma were studied and divided into two groups: patients receiving postoperative epidural analgesia with morphine (epidural group) and patients receiving postoperative intravenous analgesia with fentanyl (intravenous group).
However, as stated by the authors themselves, the epidural was not used during surgery in order to decrease the risk of awareness during anaesthesia. Since it has been reported that neuraxial analgesia reduces both the inflammatory surgical stress response and immunosuppression, the absence of epidural analgesia intraoperatively may have affected the results (284). On the one hand, surgical stress response and immunosuppression may not have been attenuated, on the other hand possible preemptive mechanisms may have been abolished (54,169).
Furthermore, different opioids were used. In the epidural group, morphine was primarily used, whereas fentanyl and tramadol were used as analgesics in the intravenous group. Although opioids have been shown to have a beneficial effect on reducing surgical stress (68-69), opioids in general and morphine in particular have been shown to affect immunity adversely (15,48-50, 52-54,57,58).

Finally, tramadol has been shown to exhibit different effects on autonomic immunity. Apart from its effects on opioid receptors, tramadol also influences the noradrenergic and serotonergic systems. In both rodent and human studies, a subsequent increase of NK-cell activity was noticed after treatment with tramadol (74). Furthermore, tramadol has been shown to prevent both surgically induced suppression of NK-cell activity as well as increase of lung metastases. In a study, in which women with endometrial carcinoma underwent hysterectomy, administration of 100 mg tramadol immediately after the operation was shown to result in an increase in NK-cell activity (75).
All of the abovementioned factors could very well have contributed to the difference in findings reported.

Based on their meta-analysis, Bell and colleagues report that local anaesthetic infiltration via wound catheters combined with patient-controlled opioid analgesia provides comparable pain relief to epidural catheters in patients undergoing open liver resections. However, pain scores were significantly lower in patients with an epidural on the first postoperative day. Both techniques were associated with similar hospital stay and opioid use with wound catheters associated with lower complication rate. Unfortunately, the type of complications was not defined (285).

In contrast with their previous study on colorectal cancer (322), Cummings et al. were unable to demonstrate an association between epidural analgesia and mortality in patients undergoing resection for gastric cancer (286). In their population-based study, patients aged 66 years or older who underwent gastric resection for non-metastatic gastric carcinoma were studied. Survival and recurrence after resection was compared between patients receiving epidural analgesia and those who did not. There was no significant difference between groups regarding treated recurrence or survival. Whether these findings are true or a result of insufficient power is reported unclear by the authors. Surprisingly, only 766 patients of the identified 2745 patients (< 28%) were reported to have received epidural analgesia.

Bouman and colleagues have studied the effects of epidural analgesia on the incidence of chronic postsurgical pain after open abdominal surgery. Based on their case-control study, the authors conclude that the combination of general anaesthesia with epidural analgesia

results in a significantly lower incidence of chronic postsurgical pain 6 months after abdominal surgery (287).

Lee and co-workers claim that the administration of a single-dose of intravenous dexamethasone in patients undergoing endoscopic submucosal dissection for gastric cancer effectively reduces epigastric pain 6 hours porstoperatively. This claim is based on their prospective, double-blinded, placebo-controlled trial in which the administration of 0,15 mg/kg intravenous dexamethasone is compared with the administration of saline-only placebo. Apart from a significantly lower pain intensity value at 6 hours postoperatively, there were no differences between both groups with respect to length of stay or complications (acute or delayed) (288).

Mohamed et al. have studied the effects of intrathecally administered dexmedetomidine on postoperative pain and analgesics consumption in patients undergoing major abdominal surgery. Based on the results of their randomized, double-blind trial, in which patients received either 10 mg bupivacaine intrathecally, or 10 mg bupivacaine plus 5 µg dexmedetomidine, or the same combination of bupivacaine and dexmedetomidine plus 25 µg of fentanyl, the authors conclude that dexmedetomidine 5 µg given intrathecally improves the quality and the duration of postoperative analgesia and also provides an analgesic sparing effect. Futhermore, the addition of intrathecal fentanyl 25 µg has no valuable clinical effect (289).
These results are confirmed by Wu and colleagues in their meta-analysis. However, it has to be mentioned that neuraxial application of dexmedetomidine was associated with an increased risk of bradycardia. No evidence showed that neuraxial dexmedetomidine increased the risk of other adverse events, such as hypotension (290).

Jiang et al. report that the neutrophil-to-lymphocyte ratio (NLR) may represent a useful prognostic index for the prediction of overall survival in patients with gastric cancer undergoing radical resection (291).
El Aziz shares the view that pre-treatment NLR is an independent prognostic factor of overall survival in patients with stage III-IV gastric cancer receiving neoadjuvant chemotherapy (FOLFOX 4) (292).

These findings are confirmed by Tanaka and colleagues. The used cut-off point for the NLR in this retrospective study was 2,5 (293).

As mentioned previously, neutrophils play an important role in carcinogenesis and tumour growth. Tokumoto and co-workers have studied the significance of neutrophils in gastric cancer progression. Based on their results, they conclude that tumour-associated neutrophils in regional lymph nodes promote the invasion of lymph nodes by gastric cancer cells via augmentation of lymphangiogenesis and thereby contribute to tumour progression (294).

Atila et al. state that NLR can provide information about inflammatory staus, tumour aggressivity and prognosis in patients with gastrointestional stroma tumours (GIST) (295).

Xiao and colleagues claim that, based on their meta-analysis, NLR is associated with poor overall survival and disease free survival in patients with hepatocellular carcinoma, initially treated by surgical resection. High NLR was also associated with poor overall survival in patients with hepatocellular carcinoma treated by radiofrequency ablation. In addition, high NLR was significantly correlated with the presence of vascular invasion and tumour multifocality (296). Unfortunately, the cut-off value for defining high NLR in the identified studies had not been unified.
Yamamura confirms these findings. Based on their prospective study on patients with hepatocellular carcinoma, the authors conclude that preoperative NLR is an independent predictor of recurrence-free survival in patients with hepatocellular carcinoma after curative hepatectomy. Furthermore, NLR proved superior to other inflammation-based prognostic scores, like the Glasgow Prognostic Score, platelet-to-lymphocyte ratio, Prognostic Index, and Prognostic Nutritional Index (297).

Neofytou, on the other hand, reports that preoperative Platelet-to-Lymphocyte ratio (PLR) is superior to preoperative NLR as an adverse prognostic factor in patients who undergo liver resection for liver-only colorectal metastases. This conclusion is based on their retrospective study in which patients with liver-only colorectal metastases were studied following neoadjuvant chemotherapy. Although both high NLR and high PLR were associated with decreased disease-free survival (DFS) and overall survival (OS) in univariate analysis, only

PLR remained significant in multivariate analysis. A NLR > 2,4 and a PLR > 150 were considered to be elevated (298).

Sugiura et al. conclude that preoperative NLR offers important prognostic information for patients with gastric outlet obstruction due to advanced pancreatic carcinoma. A higher NLR was associated with increased postoperative morbidity and shorter survival time (115). Ahmad, based on a systematic review, states that NLR may be useful as a predictor in patients with pancreatic ductal adenocarcinoma (299).
These findings are confirmed by Li and colleagues. Based on their study results, they claim that a low NLR level is associated with higher 6-month survival rate, as well as decreased incidence of ascites, portal vein thrombosis and metastasis in patients with advanced hepatocellular carcinoma (300).

Da Fonseca et al. have studied the prognostic role of NLR in patients with advanced hepatocellular carcinoma treated with sorafenib. Based on the results of their retrospective analysis they conclude that NLR affects survival in advanced hepatocellular patients treated with sorafenib. The used cut-off point for the NLR was 3.5 (301).
Terashima et al. draw the same conclusion. In their retrospective study, patients with advanced hepatocellular carcinoma treated with hepatic arterial infusion chemotherapy were studied in relation to the NLR. Low NLR (< 2.87) was clearly associated with longer progression-free and overall survival, and response to hepatic arterial infusion chemotherapy (302).

Hu and colleagues report to have developed a novel systemic-inflammation index (SII) based on lymphocyte, neutrophil and platelet counts. This index was developed based on a retrospective study, and validated in a prospective study in patients undergoing curative resection for hepatocellular carcinoma. They report that analyses revealed that SII was an independent predictor of overall survival and relapse-free survival. Therefore, the authors conclude that SII is a powerful prognostic indicator of poor outcome in patients with hepatocellular carcinoma. The used cut-off point for SII was 330 (303).

Luo and co-workers confirm the prognostic role of the NLR in patients with advanced pancreatic cancer. Furthermore, they also claim that NLR may serve as a potential biomarker for overall survival in patients with advanced pancreatic cancer undergoing chemotherapy. This claim is based on the finding that both baseline NLR and post-chemotherapy NLR change proved independent prognostic factors in overall survival. The used NLR cut-off point in this retrospective study was 3,1 (304).
Ben et al. also state that pretreatment NLR is a simple and useful biomarker for overall survival in patients with pancreatic ductal adenocarcinoma (PDAC) after curative resection. This claim is based on the results of their retrospective cohort study. PDAC patients with a high NLR (≥ 2.0) had significantly worse overall survival compared with patients with low NLR (< 2.0) (305).
Inoue and colleagues, on their turn, claim that a high NLR (≥ 2.0), and a high level of C-reactive protein, is significantly associated with worse prognosis in patients with pancreatic cancer (306).

McNamara and colleagues indorse the prognostic importance of the NLR. In their retrospective cohort study, a NLR ≥ 3.0 was clearly associated with worse overall survival in the entire cohort of biliary tract cancer patients. Furthermore, NLR proved also prognostic in patients with advanced biliary tract and hilar cancer (307).
In case of gastric cancer surgery, Graziosi and co-workers support this finding. Based on their study results, a NLR > 2.3 (median preoperative NLR) proved clearly associated with worse overall survival (308).

Ishizuka et al. confirm the prognostic value of the NLR as well, albeit in combination with the platelet count. They state that, based on their study results, the preoperative combined platelet count and neutrophil-to-lymphocyte ratio is a useful predictor of postoperative survival in patients undergoing surgery for gastric cancer (309). Li et al. also claim that NLR is an independent predictor of survival in gastric cardia adenocarcinoma (310).

Teo cum suis conclude that not only the pre-treatment NLR is prognostic of worse outcome in patients with advanced pancreatic ductal carcinoma, but also the post-treatment NLR. A persistently elevated post-treatment NLR (> 3.0) was associated with worse overall survival

compared with a decreasing, increasing or persistently low NLR. Interestingly, a quarter of the studied patients showed a > 50% decrease in NLR following 4 weeks of chemotherapy, with a trend towards improvement in overall survival (311). Apparently, an increase in post-treatment NLR was not associated with worse outcome.
This is in shrill contrast with Jin's study results. The authors conclude that in patients treated for gastric cancer, NLR before surgery is an independent prognostic factor on progression-free survival, but not on overall survival. Furthermore, post-chemotherapy (high) NLR normalized in nearly half of the patients, and this normalization was associated with better median progression-free survival and overall survival (312).
Xue, on the other hand, reports that in patients with advanced pancreatic cancer following palliative chemotherapy, NLR is an independent prognostic factor for overall survival (NLR > 5.0). Furthermore, in patients with a pre-treatment NLR of > 5.0 whose NLR dropped to ≤ 5.0 after one cycle of chemotherapy, overall survival was significantly longer compared with those whose NLR remained at > 5.0 (313).
A satisfactory explanation for these contradictory results can't readily be given. Obviously, further study results are needed.

Based on their retrospective study, Nakayama et al. conclude that preoperative NLR is a predictor of the presence of peritoneal metastasis in patients with advanced gastric cancer. In this study, a NLR > 2.37 proved an independent predictor of peritoneal metastasis in patients with advanced gastric cancer (314).
Mohri and colleagues reviewed 123 consecutive patients with gastric cancer and synchronous distant metastasis. Patient, tumour, laboratory, surgical and chemotherapy factors were analysed, with overall survival as endpoint. Apart from the pre-treatment NLR, gastrectomy, with or without metastasectomy, and carbohydrate antigen 19-9 (CA 19-9) were identified as predictors of overall survival. A pre-treatment NLR > 3.1 proved clearly associated with worse survival, whilst gastrectomy, with or without metastasectomy, was associated with better survival. In the group of patients that underwent surgery, NLR and CA 19-9 were also independent prognostic factors (315).
Xu and co-workers support these findings. In their study in gastric cancer patients, (high) NLR was clearly associated with invasion out of myometrium, low differentiation of the

tumour, tumour TNM classification, number of metastatic lymph nodes, invasive tumour depth and tumour size (316).

In their recently published paper, Call and colleagues report that, in patients undergoing resection of pancreatic carcinoma, survival was increased in patients who received perioperative epidural analgesia and/or intraoperative dexamethasone. There was a reported 44% hazard ratio reduction with intraoperative dexamethasone use (317).

4.3 We were unable to identify any study results focussing on small intestine cancer (recurrence) and its relation to anaesthesia.

4.4 Fortunately, numerous studies are reported dealing with colorectal cancer.
First of all, although intraoperative dexamethasone use has been reported to increase survival in patients undergoing resection of pancreatic carcinoma (317), this beneficial effect was not encountered in patients undergoing resection of the colon (318).

Several studies show that cyclooxygenase-2 inhibitors display distinct anti-tumour effects in colorectal malignancies. This effect involved both the primary tumour as well as its metastases (79-83).
The chemopreventive action of NSAID's is further explored by Rigas and Tsioulias (319).

The remaining studies aimed at the possible effects of thoracic epidural analgesia on survival and cancer recurrence. Gupta et al found a significant reduction in "all-cause" mortality in patients receiving epidural analgesia when compared to patients using an intravenous PCA-technique after rectal cancer surgery. Remarkably, this reduction could not be found in patients undergoing colonic cancer surgery (320). Gottschalk and colleagues found no evidence, but did observe an association between the administration of thoracic epidural analgesia and reduced probability of cancer recurrence in older patients with colorectal cancer. Interestingly, this benefit could not be found in younger patients with colorectal cancer (321).

By contrast, Christopherson cum suis found epidural analgesia to be associated with longer survival in patients undergoing surgery for colon carcinoma. However, this proved only valid in patients without metastases. In patients with metastases this association could not be demonstrated (93). A striking finding for which no clear explanation can be given.

In a large cohort study, including over 42000 patients, Cummings demonstrated that epidural analgesia was associated with an improved 5-yr survival in patients with non-metastatic colorectal cancer. A decrease in cancer recurrence, however, could not be demonstrated (322). By contrast, Myles found no association with recurrence free survival when perioperative neuraxial blockades were administered during oncological laparotomies (323). Day et al were also unable to find a difference in survival when comparing the use of postoperative loco-regional analgesia (epidural as well as spinal) to postoperative use of intravenous opioids, in patients undergoing laparoscopic colorectal resection (324). Binczak and co-workers report a trend in favour of epidural analgesia, but no statistically significant association between perioperative analgesia and recurrence-free and overall survival in patients after abdominal surgery for cancer (325).

Finally, Chen and colleagues have studied the effects of epidural analgesia on fast-track surgery in colon cancer patients. In this prospective study, 53 patients scheduled for colon cancer sesection were randomized into two groups. The first group received general anaesthesia (G group), the second group general anaesthesia combined with epidural analgesia (E group). Based on the results, the authors conclude that general anaesthesia combined with epidural analgesia plays an important role in fast-track surgery, mitigating the surgical stress-impairment of anti-tumour immune responses and hastening the recovery of intestinal function. This combination might also help to improve long-term outcomes for colon cancer patients (326).

Baptista –Hon points out that ropivacaine, an amide-linked local anaesthetic, acts as a potent inhibitor of metastatic colon cancer cell invasion, which may be beneficial during surgical resection of colon cancer (327). Other studies have confirmed that local anaesthetics exhibit anti-tumour effects (40-43).

Piegeler demonstrated that only local anaesthetics of the amide type display these inhibiting properties, in contrast to local anaesthetics of the ester type (44).
Lirk and colleagues, on their turn, report that lidocaine and ropivacaine, but not bupivacaine, demethylates deoxyribonucleic acid in breast cancer cells in vitro. This in turn reactivates tumour suppressor genes and inhibits tumour growth (45).
Herroeder shows that the systemic use of lidocaine in patients undergoing colorectal surgery leads to a decrease in inflammatory cytokine release and a shortened length of hospitalization (328).

In their prospective randomized trial, Xu et al. show that the use of epidural analgesia combined with propofol anaesthesia results in a significant decrease in serum levels of factors associated with angiogenesis during colon cancer surgery, compared to the use of volatile anaesthetics and opioids (329).

Desgranges and colleagues studied the effects of epidural analgesia during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) and found no increased risk for hemodynamic instability, meningitis or epidural abscesses in the presence of epidural analgesia (n = 35 patients) (330). These findings are confimed by Owusu-Agyemang et al. Based on their retrospective analysis the authors conclude that epidural analgesia can be safely provided to patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Interestingly, early initiation of epidural analgesic infusions (before incision) was associated with significantly less surgical blood loss and fluid requirements (331). However, volume of blood transfused, intraoperative vasopressors use, time to extubation, and length of hospital stay was not affected.

Holler and co-workers claim that peridural analgesia is positively associated with improved long-term survival in patients who undergo surgery for colorectal cancer without metastases. This claim is based on a meta-analysis (332).

Chen and Miao have performed a meta-analysis of both retrospective and prospective studies in which the effect of epidural analgesia on survival in human cancers was studied. Their results indicate that epidural anaesthesia and/or analgesia might be associated with

improved overall survival in patients with operable cancer undergoing surgery (especially in colorectal cancer) (333).

He and colleagues have studied the effects of epidural analgesia on quality of life and pain in advanced cancer patients. In this prospective study, patients diagnosed with advanced cancer who received analgesia treatment were randomly divided into two groups. One group received self-controlled epidural analgesia (EA, n=26), the other group self-controlled intravenous analgesia (IA, n=24). Visual analog scale (VAS) and Karnofsky score were used to assess pain and quality of life. Results showed that respiration and oxygen saturation in the EA group were significantly improved compared with that of the IA group. Furthermore, VAS and the Karnofsky score were significantly lower in the EA group. Patients treated with EA also felt more satisfied and experienced less complications than those treated with IA (334).

Meyhoff et al. emphasize the importance of the level of inspiratory oxygen fraction during abdominal surgery (335). Several studies have recommended using a high perioperative inspiratory oxygen fraction (80%) because of its association with lower incidence of postoperative wound infections. Meyhoff's study, on the other hand, demonstrated that administration of such a high inspiratory oxygen fraction in patients undergoing cancer surgery resulted in a significantly increased long-term mortality (2 years). Strikingly, this proved not the case in non-cancer patients.

Schietroma's prospective, randomized and double-blinded study confirms that an inspiratory oxygen fraction of 80% reduces postoperative surgical site infection in patients undergoing colorectal surgery, compared with an inspiratory oxygen fraction of 30%. In this study, patients undergoing elective open infraperitoneal anastomosis for rectal cancer who received a higher inspiratory oxygen fraction developed 41% less postoperative surgical site infections compared with the group receiving lower inspiratory oxygen fraction. The authors claim that this reduction was achieved with few risks to the patients. Possible effects on cancer recurrence and/or mortality were not mentioned (336).

By contrast, two other studies in an experimental setting showed oxygen to have suppressing effects on cancer (337,338). A satisfying explanation for these contrary findings cannot be given.

Interesting to know is that Staehr and colleagues did not find adverse pulmonary effects of long-term artificial respiration (up to 5 hours) with an inspiratory oxygen fraction of 80% compared to 30% (339).

With respect to the use of NSAID's, it should be noted that the use of both cyclooxygenase-2 selective NSAID's as well as diclofenac incorporate a potentially greater risk for anastomotic leak after colorectal resection with primary anastomosis (340).

Yauw and colleagues report, in their study involving rats, that the use of diclofenac is associated with a greater risk for anastomotic leak in case of anastomosis of the ileum and proximal colon, but not of the distal colon. Furthermore, they demonstrate that delayed treatment with diclofenac (starting 1 to 2 days postoperatively) results in a substantial decrease in anastomotic leak (341).
We believe there is sufficient evidence that suggests that the use of non-selective non-steroidal anti-inflammatory drugs may be related to a higher risk of anastomotic leakage as far as the ileum and possibly proximal colon are concerned. With respect to the distal colon, evidence is less clear. For instance, Leake et al. were unable to identify a single modifiable risk factor that contributes to anastomotic leak in colorectal surgery (342).

Turrentine et al. report that, based on their retrospective survey, anastomotic leak is associated with congestive heart failure, peripheral vascular disease, alcohol abuse, steroid use, abnormal sodium, weight loss, and location of anastomosis. Patients who experience an anastomotic leak have lower rates of survival at 30 days and long term. NSAID use was not associated with higher risk of developing anastomotic leak (343).

Hakkarainen et al, on the other hand, report that postoperative NSAID use (beginning within 24 hours after surgery) is associated with 24% increased risk for anastomotic leak.

However, this association was isolated to *nonelective* colorectal surgery! Overall, NSAID use was not associated with an increased risk of anastomotic leak (344).

Burton and colleagues were unable to detect any statistically significant difference in incidence of anastomotic dehiscence between NSAID users and non-users (345). In turn, Tortorelli at al. were also unable to identify a single prognostic parameter for risk of leakage following anterior resection of the rectum for cancer (346).

Based on their matched nested case-control study, Subendran and co-workers state that, following elective colorectal surgery, the use of any NSAID is associated with a non-significant increase in anastomotic leaks. However, the use of ketorolac was associated with a significant increase in anastomotic leakage. There was no significant association between anastomotic leakage and cumulative NSAID dose (347). This study focused on patients undergoing elective colorectal surgery (66% inflammatory bowel disease, 34% cancer).

Saleh et al. also have studied the relationship between perioperative ketorolac use and anastomotic leakage after colorectal surgery. In this retrospective analysis, 731 patients who underwent elective colorectal surgery with primary anastomosis were studied. Of these patients, 51% received no ketorolac within the first 5 days perioperatively, and 49% received ketorolac perioperatively within 5 days after surgery. The percentage of leaks was 3.3% in both groups. After adjusting for smoking, steroid use, and age, only smoking appeared to be a significant predictor of postoperative leak. The authors therefore conclude that there appears to be no significant association between perioperative ketorolac use and anastomotic leakage after colorectal surgery (348).

For a more detailed survey on the prevention, detection and treatment of colorectal anastomotic leakage (CAL) we refer to the paper by Daams and colleagues (349). In summary, CAL is a dreaded complication and is reported to have a significant mortality, ranging from 6% to 22%. Furthermore, it is also associated with worse oncologic outcome. Despite great numbers of studies investigating risk factors, surgical techniques and prevention, incidence has not reduced over the last three decades. In 2010, the reported incidence of CAL in the Netherlands was 8.7%. The following have been identified as

possible risk factors for anastomotic leakage: male gender, smoking, obesity, alcohol abuse, preoperative steroid and non-steroidal anti-inflammatory drugs use, longer duration of operation, preoperative transfusion, contamination of the operative field, case volume per centre < 20 and timing during duty hour. In case of laparoscopic colorectal surgery, body mass index, American Society of Anesthesiologists III/IV patients, tumour distance from the anal verge, tumour depth, and pelvic outlet as independent predictors for increased operative time and morbidity after laparoscopic total mesorectal excision have been mentioned as risk factors for CAL (349).

Interestingly, Qin and colleagues have performed a meta-analysis to assess the effects of preoperative radio(chemo)therapy on anastomotic leak after rectal cancer resection. They conclude that current evidence demonstrates that preoperative radio(chemo)therapy does not increase the risk of postoperative anastomotic leak after this type of resection (350).

It is obvious that non-steroidal anti-inflammatory drug use is only one of various potential risk factors contributing to the development of anastomotic leakage.

On the other hand, and as mentioned previously, the perioperative use of epidural analgesia has been shown to have a beneficiary effect on anastomotic leakage (262,263). Thoracic epidural analgesia results in vasodilatation and subsequently in a better vascularization in the direct vicinity of the anastomosis. To what extent the beneficiary anti-tumour effects of diclofenac outweigh the greater risk for anastomotic leak has not (yet) been studied, especially not in conjunction with the simultaneous use of epidural analgesia. Obviously further study results are needed. Awaiting these results and extrapolating the findings from studies focussing on the relation between inflammation and tumour growth in general, and the inflammatory degree in special in relation to the Neutrophil-to-Lymphocyte ratio (NLR), one could advocate that non-specific NSAID's could be used in patients with a high NLR provided that simultaneous thoracic epidural analgesia is administered (93-96).
In other words, given the beneficial effects of NSAID's on tumour evolution, we do believe that totally banning their use could prove unwise in the long term. Since there is relatively little evidence showing that the use of NSAID's is directly correlated with a substantially greater risk of anastomotic leak in colorectal surgery, we believe that its use in colorectal

surgery is justifiable. Especially in case thoracic epidural analgesia is administered simultaneously.
In case of anastomosis of the proximal colon or the ileum, the use of NSAID's in conjuction with thoracic epidural analgesia should be evaluated on an individual basis (351). In case of a high preoperative NLR, we would advise to initiate treatment with NSAID's 24 hours postoperatively (340,343). In case of a low NLR, and anastomosis of the ileum, the use of NSAID's remains arguable. We support the view that caution is needed when prescribing NSAID's to patients with pre-existing risk factors for anastomotic leak (352). In our opinion, the presence of thoracic epidural analgesia should be taken into account in deciding whether or not to prescribe NSAID's.

Furthermore, it must be stressed that intraoperative volume resuscitation should focus on goal-directed euvolemia since evidence exists showing that fluid overload, in the presence of an epidural, may be deleterious to the healing of anastomoses, thus creating a higher risk of anastomotic leakage (353).

Since anastomotic leakage is associated with higher recurrence rates after colorectal surgery, Alonso and colleagues have investigated the inflammatory and angiogenic responses in patients undergoing surgery for colorectal cancer who had postoperative intra-abdominal infection, and compared the results with patients without complications.
In their prospective matched cohort study, consecutive patients undergoing surgery for colorectal cancer with curative intent were included. Patients who had anastomotic leak or intra-abdominal abscess were included in the infection group, and matched with patients who had an uncomplicated postoperative course. Interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) levels were measured in serum and peritoneal fluid. Results showed that serum IL-6 concentration was higher in the infection group on day 4. IL-6 in peritoneal fluid was higher in the infection group at 48 hours postoperatively and day 4. Serum VEGF was higher in the infection group on day 4. Peritoneal VEGF was also higher in the infection group at 48 hours postoperatively and day 4. Two-year recurrence rate was higher in patients with infection. Based on these results, the authors conclude that intra-abdominal infection increases IL-6 and VEGF after surgery for cancer. Amplification of inflammation and angiogenesis might be one of the mechanisms responsible for the

higher recurrence rate observed in patients with anastomotic leakage or intra-abdominal abscesses (354).

As mentioned previously, several studies suggest that cyclooxygenase-2 inhibitors display distinct anti-tumour effects in colorectal malignancies. This effect involves both the primary tumour as well as its metastases (79-83).
In view of these findings, Johnson et al. have conducted a population-based retrospective cohort study in which patients with colorectal cancer (less than stage IV) and no history of Crohn disease, ulcerative colitis, and irritable bowel disease were studied in relation to NSAID use, cancer recurrence and survival. Results showed that NSAID users had a 3-fold decreased risk of colorectal cancer recurrence and a > 7-fold decreased risk of death. Therefore, the authors conclude that these results suggest that current use of non-steroidal anti-inflammatory drugs provides significant improvements in colorectal cancer outcomes (355).

Wang et al. have studied the association between NSAID's use and colorectal cancer. Based on the results of their cohort study, in which almost 73.500 individuals were included, they report that high use of any type of NSAID was significantly associated with a lower risk of colorectal cancer. Furthermore, NSAID use was associated with a greater risk reduction of proximal colon cancer versus distal colon cancer (356).

Tougeron and co-workers expand further on the relation between aspirin use and colorectal cancer (357).

Recently, Kubo and colleagues have published their study results on the importance of the NLR in relation to the long-term survival following resection of colorectal carcinoma. Based on their retrospective study, they claim that NLR is an independent predictor of survival in colorectal cancer. Not only the preoperative NLR proved prognostic, but also the postoperative NLR was significantly associated with cancer-specific survival. The disease-free survival was significantly longer in patients with a low preoperative NLR. Cancer-specific survival was significantly longer in the group with a low NLR on the third

postoperative day. A high postoperative NLR, on the other hand, proved to be an independent risk factor for both cancer-specific survival and disease-free survival (111).

Azab and co-workers confirm the importance of the pre-treatment NLR in predicting the long-term survival in colorectal cancer (358). Based on their longitudinal retrospective study, the authors claim that elevated pre-treatment NLR is an independent predictor of both worse overall and disease free survival in colorectal cancer. The platelet-to-lymphocyte ratio, however, proved non-predictive of mortality in colorectal cancer.

Ying et al. also have studied the prognostic value of preoperative NLR for predicting clinical outcome in surgical colorectal cancer patients. Based on the results of their study, they conclude that elevated NLR is an independent factor for poor recurrence-free survival, overall survival, and cancer-specific survival. Unfortunately, the NLR cut-off point was not mentioned (359).

Formica cum suis have come to same conclusion regarding the adverse prognostic value of a high baseline NLR in patients with metastatic colorectal cancer treated with standard first-line chemotherapy (FOLFIRI-Bev: Fluorouracil, Irinotecan and Bevacizumab). However, among patients with stable disease, the prognostic effect of NLR changed after two cycles of chemotherapy. In treated patients, an increase or preservation in NLR was clearly associated with a significant reduction in the risk of death compared with patients with a decreased NLR (360).
Apparently, in this study a high NLR before chemotherapy appears to be associated with more aggressive disease and (potentially) worse outcome. In contrast, a high NLR after chemotherapy appears to be associated with better outcome.

As discussed earlier, Teo et al. reported similar findings (311). Based on their study, they conclude that a persistently elevated post-treatment NLR (> 3.0) is associated with worse overall survival compared with a decreasing, increasing or persistently low NLR. In other words, in patients with advanced pancreatic ductal carcinoma who had been treated with chemotherapy, a persistently elevated post-treatment NLR (> 3.0) was associated with worse overall survival compared with a decreasing, increasing or persistently low NLR.

Apparently, an increase in post-treatment NLR was not associated with worse outcome. A satisfactory explanation for these findings can't readily be given. Obviously, further study results are needed.
This is in shrill contrast to the results published by Luo and colleagues (304). In their study, both baseline NLR and post-chemotherapy NLR change proved independent prognostic factors in overall survival. The used NLR cut-off point in the retrospective study was 3,1. A high NLR pre- and post-chemotherapy were associated with worse outcome.
Chua and co-workers support the importance of a decrease in NLR after chemotherapy. In their paper, they report that normalisation of NLR after one cycle of chemotherapy in patients with advanced colorectal cancer resulted in improved progression-free survival (361).
Dirican's other retrospective study shows that in patients with metastatic colorectal cancer treatment with bevaciumzab is associated with a lower NLR, and longer overall and progression-free survival (362).

Interestingly, Peng et al. claim that not a high NLR, but an increase in NLR (ΔNLR) following curative resection for hepatocellular carcinoma, is an independent prognostic factor for overall survival and recurrence free-survival. This claim is based on their retrospective cohort study involving 189 patients with hepatocellular carcinoma who underwent curative resection. Patients were divided into two groups: Group 1: increased NLR; Group 2: decreased NLR. Demographic and clinical data, overall survival and recurrence free-survival were compared (363).

Based on their prospective cohort study, Cook and co-workers claim that postoperative NLR predicts complications following colorectal surgery (364). Elective colorectal resection was associated with an increase in mean NLR from 3.5 to 11.6. Patients with a NLR $\geq$ 9.3 on the first postoperative day had a significantly greater risk of complications. In view of these findings, the authors conclude that NLR helps to identify patients at high-risk of complications, allowing targeted preventive measures.

Kilincalp et al., on their turn, conclude that NLR, platelet-to-lymphocyte ratio (PLR) and mean platelet volume (MPV) may be used as easily available additional biomarkers for

colorectal cancer (CRC) in screening the general population, as well as in postoperative follow-up. This claim is based on the results of their study in which 144 CRC patients and 143 age-matched and sex-matched healthy participants were investigated. NLR, PLR and MPV were significantly higher in CRC patients preoperatively, compared with healthy participants. Receiver-operating characteristic curve analysis suggested 2.02 as the cut-off value for NLR (sensitivity 86%, specificity 84%). Surgical tumour resection resulted in a significant decrease in NLR, PLR and MPV (365).

Finally, Tohme's study results indicate that NLR is also prognostic for survival in case of radioembolization for metastatic colorectal cancer (484).

Based on their meta-analysis, Malietzis and colleagues claim that a high pre-treatment NLR independently predicts worse outcome in patients treated for colorectal cancer. This proved the case in patients undergoing surgery, but also in patients undergoing palliative chemotherapy and treatment for colorectal liver metastases (366).

Kim et al. have studied the predictive value of NLR in patients with rectal cancer undergoing preoperative chemoradiation. Based on the results they conclude that high NLR (≥ 3.0), an elevated carcinoembryonic antigen level (CEA), and large tumour were significant predictors for a poor response. Poor pathological tumour response and elevated NLR (≥ 3.0) were risk factors for cancer-specific and recurrence-free survival (367).
Shen and colleagues support the claim that an elevated baseline NLR is a valuable and easily available prognostic factor for overall survival in addition to tumour response after neoadjuvant chemoradiation in patients with locally advanced rectal cancer. In this retrospective study, a NLR < 2.8 was significantly associated with better overall survival (368).
These findings are confirmed by another meta-analysis performed by Paramanathan et al. (105).

Based on earlier study results, He and co-workers have built a prognostic model on blood-based biomarkers, including NLR, in patients with metastatic colorectal cancer. This model

is based on three previously identified independent risk factors: NLR (> 3.0), elevated γ-glutamyl transpeptidase and carcinoembryonic antigen, but has not been validated yet (369).

Ikeguchi et al. report similar findings. Their newly developed prognostic scoring system, consisting of performance status (PS), Glasgow Prognostic Score, Prognostic Nutritional Index, and NLR, proved prognostic of survival in patients with locally advanced unresectable colorectal cancer undergoing intensive chemotherapy (370).

Interestingly, Sun and colleagues claim that pretreatment fibrinogen levels also can serve as an independent prognostic marker to evaluate patient response to surgical colon cancer treatment. The results of their retrospective analysis revealed that preoperative fibrinogen levels < 2.61 were significantly associated with better overall survival and disease-free survival compared with fibrinogen levels ≥ 2.61 (371).
As is well known, fibrinogen is synthesized in the liver as a glycoprotein and plays an important role in blood coagulation, thrombosis, wound healing, and platelet aggregation. Recent studies suggest that fibrinogen may be associated with cancer development. Fibrinogen has been associated with increased tumour growth and metastatic potential, albeit the exact mechanisms remain unclear. Various potential mechanisms have been put forward. One mechanism involves the influence on tumour cell proliferation, migration and signalling through interactions with multiple, so-called, integrin and non-integrin receptors (transmembrane receptors).
Another potential mechanism is the promotion of tumor angiogenesis, since fibrinogen has been shown to interact with growth factors, including vascular endothelial and fibroblast growth factors, to stimulate angiogenesis. Furthermore, the fibrinolytic system derived from fibrinogen also plays a facilitating role in both angiogenesis and the proliferation process of tumor cells.
For more comprehensive information on the role of fibrinogen on cancer development we refer to the paper by Sun et al. (371).

Mariani et al. expand further on the significance of inflammation in the development of colorectal cancer (372). In their paper, the authors evaluate the most important inflammatory pathways involved in the very early steps of (colorectal) carcinogenesis. They

focus on cells and proteins that are suggested to play a key role in the mechanisms leading to tumour development. Furthermore, the tumour microenvironment and its oxidative and anaerobic metabolisms are identified. First of all, the role of macrophages, neutrophils and the two groups of enzymes, the cyclooxygenases (COX-1 and COX-2) and the lipoxygenases (5-lipoxygenase [5-LOX], 12-LOX, and 15-LOX), are discussed.

In summary, Type I macrophages have been identified to play a role in killing pathogens and tumour cells by producing large amounts of pro-inflammatory cytokines, like tumour necrosis factor-α (TNF-α), interleukin (IL)-12, reactive nitrogen, and oxygen intermediates. Not surprisingly, these macrophages are often found in chronic inflammatory sites, and sites where tumours originate.

Type II macrophages, on the other hand, are believed to play a role in the modulation, c.q. moderation of the inflammatory response and are generated by various interleukins (IL-4, IK-13, IL-10) and glucocorticosteroid hormones. Furthermore, type II macrophages also play a role in eliminating cell debris, promoting angiogenesis, remodelling tissue and releasing other cytokines, like IL-10. As discussed previously in the case of Epithelial Mesenchymal and Mesenchymal Epithelial Transitions, it is possible that type I macrophages switch to a type II-like phenotype. Thus facilitating the tumour to grow, invade, vascularize and develop.
Once pro-inflammatory cytokines have been produced and released, including the rapidly produced IL-23, neutrophils are swiftly attracted to the site of infection. Normally, neutrophils are phagocytosed by macrophages after transmigration and apoptosis. Phagocytosis of apoptotic cells might down-regulate the production of IL-23 and thus inhibit the invasion by neutrophils. In case this feedback is interrupted, macrophages would continue to attract neutrophils and result in an overexpression of neutrophils at the tissue site.

Neutrophils are activated by inflammatory signals. Once activated, these cells are able to produce and release pro-inflammatory mediators, such as IL-1, IL-8 and macrophage inflammatory protein (MIP)-1s. In addition, neutrophils also synthesize and store large quantities of enzymes, like for instance myeloperoxidase (MPO). The aforementioned

cytokine IL-23 further activates neutrophils to synthesize and release these enzymes. Thus, resulting in tissue destruction through proteolysis.
When this has been achieved, neutrophils change their phenotype from a pro-inflammatory state into a more "anti-inflammatory pro-resolution" state. These apoptotic neutrophils on their turn stimulate macrophages into a pro-resolution state. As stated by the authors, the resolution of inflammation therefore relies on the effective "switching off" of the neutrophils, the promotion of apoptosis and the successful recognition of phagocytosis.
There is evidence that suggests that the enzyme myeloperoxidase (MPO), which is synthesized and released by activated neutrophils, indeed can promote neutrophil survival. By contrast, the cytokines IL-10 and TNF-α are able to induce apoptosis. In case of persistent inflammation, this regulatory mechanism can easily be compromised. Accordingly, in patients with colorectal cancer, a low level of persistent inflammation has been demonstrated to exist in normal colorectal mucosa (373). Without inhibitory feedback, neutrophils will continuously be attracted and will accumulate in the intestinal mucosa. Apoptotic neutrophils that have not been eliminated by macrophages will undergo secondary necrosis. This will result in a release of toxic substances leading to further pathological tissue damage.

Arachidonic acid is formed by the interaction between the enzyme phospholipase A2 and fatty acid compounds derived from membrane phospholipids, the so-called prostanoids and eicanosoids. Despite the fact that these compounds are considered to be paracrine hormones, and hence their effects are rather localized, their release can have pronounced effects. Although primarily related to inflammation and hemostasis, all of these compounds display vasoactive effects, mostly by influencing vascular tone.
Arachidonic acid on its turn is metabolized, either by the cyclooxygenase (COX) or the lipoxygenase (5-LOX, 12-Lox and 15-LOX) pathway.
There are different forms of the COX-enzyme, COX-1 and COX-2 being the most important ones. COX-1 is more fundamental and therefore capable of producing prostanoids under basal conditions. By contrast, COX-2 is inducible and upregulated during inflammation. Eicanosoids, which are derived from arachidonic acid, are among the earliest signals released in response to an inflammatory stimulus or injury.

The COX pathway in metabolizing arachidonic acid contributes to the accumulation of neutrophils and the production of Prostaglandin E2 (PGE2). COX-2 appears to be overexpressed in both tumour cells and immune suppressor cells, like for instance macrophages. The increase in PGE2 production mediated by the overexpression of COX-2 has been shown to promote colorectal carcinogenesis (374).

The LOX pathway is also closely linked to chronic inflammation and carcinogenesis. 5-LOX is highly expressed in neutrophils and monocytes. Following cell activation, arachidonic acid released from membrane phospholipids is converted by 5-LOX into leukotriene B4 or leukotriene C4. Both of these have been shown to be linked to early colon cancer growth and proliferation (375).

12-LOX metabolites are reported to promote cancer cell proliferation, metastasis, and angiogenesis, whereas 15-LOX metabolites seem to be protective against inflammation and carcinogenesis. Furthermore, the LOX-15 pathway appears to play an important role in the resolution of inflammation. 15-LOX enzymes are usually expressed in normal tissues and benign lesions, but not in colon cancer cells (376,377).
On the other hand, 5-LOX and 12-LOX are generally absent in normal healthy epithelia, but can be induced by pro-inflammatory stimuli and are expressed in various epithelial cancers (378).

It is obvious that a chronic infection will lead to a chronic inflammatory response. In case of any imbalance between active inflammation, repair and destruction caused by a persistent stimulus over a prolonged period of time, the inflammatory response, and its activation of immune cells, will result in an accumulation of cytokines, chemokines and reactive oxygen and nitrogen species. Further imbalance between endogenous generation of reactive species and anti-oxidant and scavenging defence mechanisms will result in oxidative stress. This will lead to oxidation of several substances, like nucleic acids, proteins and lipids, and will induce pro-mutagenic DNA lesions (372). The authors claim that reactive oxygen species originating from chronic inflammatory cells may play a central role in the development of up to one-third of all cancers. Especially neutrophils and macrophages are considered to be

a major source of oxidants that may promote cancer development through the induction of genetic alterations.
Inflammation sites are associated with changes in structure, function and activity of mitochondria. Through the production of reactive oxygen species an oxidative microenvironment is created which results in DNA damage, and shifting from an aerobic to an anaerobic metabolism. This anaerobic metabolic process may lead to alterations in glucose uptake and lactic acid production. And this may result in further DNA damage.

For more comprehensive information on this topic, we once more refer to the paper by Mariani and colleagues (372).

Lalmahomed et al.'s study results support the above-mentioned mechanisms of action. Altough circulating tumour cells were identified in 43% of the samples of peripheral blood that had been withdrawn preoperatively in patients with colorectal cancer with isolated liver metastases, no relation was found between the presence of circulating tumour cells in peripheral blood and disease-free and overall survival. In other words, it appears that the presence of tumour cells in the bloodstream is more commonly encountered than anticipated. Furthermore, the presence of circulating tumour cells in peripheral blood did not automatically lead to worse disease-free and overall survival. Apparently, the bodys own defence mechanisms are capable of eliminating circulating tumour cells more often than expected. This fits in with the concept that perioperative care should focus on preserving patient's immunity and defence mechanisms (379).

With respect to the function of neutrophils, Sagiv and co-workers report that three distinct populations of circulating neutrophils have been identified. Apart from the mature high-density neutrophils (HDNs), a heterogenous subset of low-density neutrophils (LDNs) has been identified which are reported to appear transiently in self-resolving inflammation but accumulate continuously with cancer progression. LDNs display impaired neutrophil function and immunosuppressive properties, characteristics that are reported to be in sharp contrast to those of HDNs (380).

Interestingly, Yan et al. report that human polymorphonuclear neutrophils (PMNs) from some healthy donors display potent cancer-killing properties. This killing activity appears to be cancer cell-specific since PMNs did not kill primary normal epithelial cells or an immortalized breast epithelial cell line. Furthermore, PMNs from lung cancer patients were als found to exhibit relatively poor cancer-killing activity compared to the cytolytic activity of the average healthy donor (381).

Park and colleagues compared the effectiveness of transversus abdominis plane (TAP) block with local infiltration of the surgical wound in patients undergoing laparoscopic colorectal surgery. Based on the results of this non-randomized, single-blind prospective study the authors conclude that bilateral TAP blocks decrease the cumulative morphine use at 24 hours and 48 hours postoperatively compared with local anaesthestic wound infiltration. In this study, patients in the TAP group received bilateral TAP blocks *at the end of surgery*. Patients in the infiltration group received local infiltration of anaesthetics in the surgical wounds after closure of the peritoneum. All patienst received postoperative analgesia with morphine as a patient-controlled analgesia (382). Needless to mention, any pre-emptive mode af action has been ruled out by the administration of the blocks at the end of surgery.

Bashandy and Elkholy have studied the effects of an ultrasound-guided preemptive single-injection rectus sheath block on postoperative pain in patients undergoing abdominal cancer surgery with midline incision. Based on their randomized controlled trial, they claim that ultrasound-guided rectus sheath block is an easy technique to learn, and when it is used with general anaesthesia, it is more effective in reducing pain scores and opioid consumption compared with general anaesthesia alone (383).

Godden et al. have compared the effects of epidural analgesia (EA) and ultrasonography placed rectus sheath catheters (RSC) on analgesia following open colorectal cancer surgery. Based on their retrospective study, the authors claim that the use of ultrasonography guided RSC results in effective postoperative analgesia equivalent to EA, with the potential benefits of a reduced incidence of hypotension. There was no significant difference in postoperative respiratory tract infection, anastomotic leak or wound complications between

the EA-group and the RSC-group. The latter group had a higher incidence of ileus than the EA-group (384).

As mentioned previously, recent studies have suggested an association between β-adrenergic receptor stimulation and cancer growth and cancer progression.
Jansen and colleagues have conducted a population-based cohort study in which the association between beta-blocker use and colorectal cancer prognosis was investigated. Results showed that beta –blocker use was associated with longer overall survival in stage IV patients. However, no significant association was observed between beta-blocker use at diagnosis and prognosis for all disease stages combined (385).

Based on their retrospective chart review, Engineer at al. report that an association was observed between exposure to a combination of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β-blockers and increased survival, decreased hospitalizations, and decreased tumour progression in advanced colorectal cancer (386).

Interestingly, Liu et al. have studied the effects of chronic stress on anti-angiogenesis of sunitinib in mouse colorectal cancer models. Their results showed that chronic restraint stress markedly weakened the efficacy of sunitinib, primarily through promoting the expression of vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) to stimulate tumour angiogenesis in vivo. As reported, this effect could be sufficiently mimicked by exogenous norepinephrine and blocked by the β-antagonist propranolol. Therefore, the authors conclude that these findings suggest that psychological stress might attenuate anti-angiogenic therapy primarily through activating β-adrenergic signalling to promote tumour angiogenesis. It is also suggested that β-blockers might improve anti-angiogenic outcome under psychological stress (387).

As mentioned previously in the case of anastomotic leak, intraoperative volume resuscitation should focus on goal-directed euvolemia, since evidence exists showing that fluid overload, in the presence of an epidural, may be deleterious to the healing of anastomoses, thus creating a higher risk of anastomotic leakage (353).

Following on from this, Volta et al. have studied the effects of two different strategies of fluid administration on inflammatory mediators, plasma electrolytes and acid/base disorders in patients undergoing major abdominal surgery for bowel cancer. Results of this prospective, double blind, randomized trial revealed that patients who were administered balanced solutions, like for instance Ringers lactate, exhibited higher circulating levels of IL-10 and TIMP-1 and lower level of active metalloproteinase 9. On the contrary, patients who were administered unbalanced solutions, like normal saline, experienced hyperchloremia, hypocalcemia, hypomagnesemia, worse acid-base equilibrium and higher level of neutrophil gelatinase-associated lipocalin. Therefore, the authors conclude that the use of balanced solutions was responsible of less alteration of plasmatic electrolytes, acid-base equilibrium, kidney function and it might be associated with an early anti-inflammatory mechanisms triggering (388).

5 Urogenital malignancies

5.1 Bladder / Renal carcinoma
5.2 Prostate / Testicular / Penile carcinoma
5.3 Ovarian carcinoma
5.4 Cervical carcinoma
5.5 Vulvar carcinoma

5.1 Bladder / Renal cancer

Only one study could be identified dealing with renal cancer in relation to anaesthesia. Benzonana et al. report that based on an in vitro study, the volatile anaesthetic isoflurane facilitates renal cancer growth by enhancing the malignant and metastatic potential of renal cancer cells (389).

With respect to bladder cancer, Tekgül et al. claim that the addition of obturator nerve block (ONB) to spinal anaesthesia in patients undergoing transurethral resection (TUR-B) results in a prolonged time to recurrence and increases the chance to lengthen disease-free survival. In this retrospective study, patients with low-risk superficial bladder tumours received either spinal anaesthesia, or spinal anaesthesia combined with ONB. Recurrence rates and disease-free time to recurrence were analyzed. Results revealed a significantly higher mean time to recurrence in patients who had received a obturator nerve block (390).

Based on the results of their retrospective study, Mazul-Sunko and colleagues claim that thoracic epidural analgesia may have specific advantages in patients with invasive bladder cancer undergoing radical cystectomy. Patients undergoing cystectomy under combined epidural-general anaesthesia had significantly less blood loss, due to induced hypotension, compared with patients who underwent cystectomy under opioid based general analgesia. Consequently, blood transfusion requirements were also lower in the epidural group. Furthermore, the incidence of ileus was also reported significantly lower in the epidural group compared with the opioid-based general anaesthesia group (391).

Forget et al have performed an observational study in early breast, lung and kidney cancer surgery in which the prognostic significance of the neutrophil-to-lymphocyte ratio (NLR) and the impact of intraoperative NSAID's was investigated. Based on the results, they conclude that NLR is a strong perioperative prognostic factor for breast, lung and kidney cancers. In this context, intraoperative NSAID's administration could be associated with a better outcome (392).
Kaminska and co-workers endorse the importance of prostaglandin E2 in renal cell cancer development (393).

Mano and colleagues report that the NLR is an independent predictor of disease progression and recurrence in patients with non-muscle-invasive bladder cancer (104). In their retrospective cohort study, 107 consecutive patients with non-muscle-invasive bladder cancer (NMIBC), treated with transurethral tumour resection, were reviewed. They found an association between high NLR levels and male sex, T1 tumour category, and high tumour grade. Furthermore, on multivariate analyses, adjusted for European Organization for Research and Treatment of Cancer (EORTC) risk groups and treatment with bladder instillation, NLR > 2.41 and > 2.43 proved significant predictors of disease progression and recurrence, respectively.
To predict outcomes, the European Organization for Research and Treatment of Cancer (EORTC) risk table is used, which uses a scoring system based on previous recurrence rate, tumour number, tumour diameter, T category, World Health Organization (WHO) grade, and the presence of concurrent carcinoma in situ (CIS), to estimate the risk of disease recurrence and progression at 1 and 5 years (394).

Vliers et al. confirm the prognostic value of NLR in patients with localized clear cell renal carcinoma undergoing nephrectomy. In their study, a NLR $\geq$ 4.0 was significantly associated with worse 5-year cancer-specific and overall survival. The median follow-up was 9.3 years (112).

Kaynar concludes that NLR can be used to determine tumour invasiveness as a cost-effective, common and simple biomarker in bladder cancer (395).

Hermanns states that NLR is an inexpensive prognostic biomarker for patients undergoing radical cystectomy for urothelial carcinoma of the bladder. Based on their retrospective cohort study, patients with a NLR ≥ 3,0 had significantly worse survival outcomes: overall survival, recurrence-free survival and cancer-specific survival (396). This conclusion is supported by Ku and colleagues (397).

De Giorgi cum suis even claim that NLR is of prognostic significance in patients with unresectable or metastatic urothelial carcinoma treated with first-line chemotherapy. Based on their retrospective study, the authors conclude that an increased NLR (> 3,0) persistent during first-line chemotherapy is an independent predictive factor for patients with advanced urothelial cancer. A high NLR pre- and post-treatment was clearly associated with worse outcome (398-400).
Park et al. have studied NLR as a prognostic factor in patients with metastatic clear renal cell carcinoma receiving sunitinib as first line therapy. Median follow-up duration after treatment was 24 months. There was no association between pre-treatment NLR and tumour response. However, lower post-treatment NLR and larger reduction in NLR after treatment was significantly associated with a better tumour response. Post-treatment NLR was also associated with cancer-specific mortality (401).

Temraz and colleagues have studied the lymphocyte-to-monocyte ratio (LMR) in patients with bladder cancer undergoing radical cystectomy and conclude that the LMR is an easily measured and inexpensive prognostic marker. In their retrospective analysis, LMR proved significantly correlated with overall survival and time to treatment recurrence (402).

Dalpiaz confirms the prognostic properties of NLR in upper urinary tract cancer patients undergoing radical surgery. In this retrospective cohort study preoperative NLR was clearly associated with cancer-specific and overall mortality (403).

In patients with upper tract urothelial carcinoma who underwent radical nephroureterectomy NLR was associated with cancer-specific and overall survival (404), and disease recurrence and cancer-specific mortality (405). In the first study, combining preoperative NLR with erythrocyte sedimentation rate improved prognostic value even more. In this study, high

preoperative NLR was defined as ≥ 2.5. In the latter study, elevated preoperative NLR was defined as NLR > 3.0.

Gunduz and colleagues confirm the importance of pretreatment NLR as a prognostic factor in metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. The results of their retrospective analysis demonstrate that only pretreatment NLR, apart from calcium levels, was significantly associated with progression free survival. Median progression free survival was significantly lower in patients with a posttreatment NLR > 2.0 compared with patients with a posttreatment NLR of ≤ 2.0 (406).

Additionally, Yilmaz et al. report that NLR is superior to C-reactive protein (CRP) and white blood cell count (WBC) for predicting the development of of acute kidney injury (AKI) in patients with severe sepsis. In this retrospective study, 118 consectutive patients with severe sepsis admitted to the ICU were enrolled and CRP, and WBC were recorded on admission and patients' renal function was monitored for 7 consecutive days. Results showed that NLR levels were significantly higher in the group that developed AKI than in the non-AKI group. AKI development was independently associated with NLR, Acute Physiology and Chronic Health Evaluation II (APACHE II) and duration of invasive ventilation. The cut-off value of 10.15 for NLR had the highest validity for predicting AKI in patients with severe sepsis. The sensitivity, specificity, negative-predictive value, and positive predictive value for this cut-off value was 90,2%, 92,9%, 90,4%, and 92,7%, respectively (407).

These findings support the hypothesis that the inflammatory stress response is a common pathway through which the body deals with different kinds of threats affecting the integrity of the body.

Although there is some evidence that perioperative intravenous lidocaine administration might reduce the requirement of opioids, improve bowel function and shorten the length of hospital stay, Wuethrich and colleagues were unable to confirm these findings. In their randomized double-blind, placebo-controlled study, systemic perioperative administration

of lidocaine over 24 hours did not influence any of the above mentioned. The inflammatory and stress response were also not influenced after laparoscopic renal surgery (408).

5.2 Prostate/ Testicular cancer

Carcinoma of the prostate is (one of) the most common malignancy (-ies) in men. In spite of this, relatively few study results have been published with contradictory results.

For instance, Biki and Forget found lower probability of carcinoma recurrence when epidural analgesia was given instead of intravenous opioids during radical prostatectomy. In both retrospective studies, postoperative levels of biochemical markers were studied, the so-called prostate specific antigen (409,410).

Scavonetto concludes that, based on their large retrospective analysis, regional anaesthetic techniques (with hydrophilic opioids) may have a possible beneficial effect on oncological outcomes after prostate surgery for cancer (411). Interestingly, the same group reports that, based on their retrospective non-randomized matched cohort study, postoperative epidural analgesia with fentanyl is not associated with improvement in oncologic outcome compared with general anaesthesia with systemic opioids in patients undergoing radical prostatectomy for cancer (412).
In the latter study, patients were divided into two groups: one group receiving general anaesthesia with systemic opioids for analgesia, the other group receiving lumbar epidural anaesthesia and analgesia with fentanyl. In the epidural group, patients were treated with amide-linked local anaesthetics and fentanyl intraoperatively. During the operation patients also received sedation with (small doses of) fentanyl and/or midazolam. Postoperatively, epidural analgesia was provided via continuous infusion of fentanyl (70-100 μg/hour) for 1 to 3 days postoperatively. The authors claim that the lack of improved oncologic outcome in the epidural group is caused by the fact that a lipophilic opioid was used. Lipophilic opioids administered in the epidural space are known to undergo rapid systemic uptake and thus induce analgesia via supraspinal rather than spinal mechanisms. Since systemically administered opioids have been shown to induce a prolonged suppression of immunity, no

opioid sparing effect and consequently no “expected” improved oncologic outcome was achieved. By contrast, in their previous study, hydrophilic opioids were used. These are known to remain in the epidural space (for a longer time) and therefore lead to a reduction of opioid consumption and subsequently result in improved outcome.

Tsui and Wuethrich were also not able to demonstrate any beneficial effects of epidural blockades in relation to cancer recurrence in their (relatively small) studies in patients undergoing radical prostatectomy (413,414). The same holds true for the adjunctive use of spinal anaesthesia on outcome in two other studies (415,416).

Despite these inconsistencies, Corsia and colleagues point out the importance of regional anaesthesia, avoiding pain and stress and reducing opioid consumption (417).

Forget in his paper offers a possible explanation for these contradictory results. In general, prostate cancer is regarded as a cancer with a low to medium malignancy grade. The Gleason scoring system is traditionally used to grade prostate cancer. Broadly speaking, prostate cancer in older men tends to behave less aggressively than in younger men. Less aggressive prostate cancer also appears to be associated with a lower inflammatory grade, as expressed by a lower NLR (Neutrophil-to-Lymphocyte Ratio). By contrast, more aggressive types of prostate cancer appear to be associated with a higher inflammatory grade, a higher NLR. In case of breast cancer, the inflammatory grade has been shown to be a determinant factor in the success of (anti-tumour, anti-inflammatory) treatment. Accordingly, in patients with breast cancer and a high preoperative NLR (≥ 4), the use of NSAID’s was associated with a reduction of the relative risk of cancer recurrence and mortality by more than 50%, compared to patients with a NLR < 4. In other words, breast cancer patients with a high NLR, a higher inflammatory grade and probably more aggressive cancer, profited most of the anti-inflammatory treatment with diclofenac (92).
This theory is supported by the results from the REDUCE study. In this study, the use of aspirin and/or NSAID was significantly associated with decreased total and high-grade prostate cancer risk, but not with low-grade prostate cancer risk (120).

In other words, the grade of inflammation appears to have predictive value in determining how successful anti-inflammatory treatment will be in reducing the inflammation, and consequently the outcome after the surgical procedure. Therefore, study results could very well be affected by the diversity of studied tumours with respect to their inflammatory grade, malignancy and consequently response to treatment.

Dell'Atti, Wang and Bhindi confirm the chemoprotective effects of anti-inflammatory drugs on prostate cancer (418-420). Furthermore, Bhindi et al. report that men who develop elevated prostate-specific antigen (PSA) levels while on NSAID's may be less likely to have an inflammatory aetiology and more likely to harbour prostate carcinoma. In other words, men who develop elevated PSA while on NSAID's, and undergo biopsy have an elevated probability that prostate cancer is detected. Therefore, it may be warranted for clinicians to consider the influence of NSAID's when evaluating patients being considered for biopsy (420).

Templeton cum suis conclude that, based on their cohort study, the NLR can be used as a good prognostic score for metastatic castration-resistant prostate cancer (113). A high NLR (> 3.0) was clearly associated with worse overall survival.

Langsenlehner et al. confirm the prognostic relevance of NLR in patients with prostate cancer. In their retrospective cohort study a NLR ≥ 5.0 was significantly associated with worse distant metastases-free survival, clinical progression-free survival and overall survival (421). Tanik even claims that NLR can predict benign prostate hyperplasia (422).

As mentioned previously, Huang and co-workers claim that strong evidence exists that isoflurane should not be used in prostate cancer surgery, in contrast to propofol. This claim is based on the finding that isoflurane enhances cancer cell characteristics associated with malignancy in exposed prostate cancer cells. In other words, prostate cancer cell line (PC3) exposed to isoflurane showed characteristics associated with malignancy with an increase of proliferation and migration, as well as development of chemoresistance. Exposure to propofol, on the other hand, resulted in partial reduction of cancer cell malignant activities (32).

Pond et al. report that baseline NLR is significantly associated with survival in patients with locally advanced penile squamous cell carcinoma who received concurrent chemo- and radiotherapy (423).
Lorente et al. report similar findings. In their study, focussing on patients with metastatic castration-resistant prostate cancer, pretreatment NLR was associated with overall survival and response to treatment with second-line chemotherapy. Furthermore, this association was independent of pretreatment corticosteroid use. In other words, patients with high NLR (≥ 3.0) had lower response to treatment and overall survival. Conversion from high to low NLR (< 3.0) after treatment was associated with improved survival (424).

Van Soest and co-workers report comparable results in patients with metastatic castration-resistant prostate cancer receiving first-line chemotherapy. The reported NLR cut-off value was 2.0 (425).

Finally, Grytli and colleagues have studied the association between β-blocker usage and prostate cancer-specific mortality. Based on the results of their observational cohort study, the authors conclude that the usage of β-blockers is associated with reduced prostate cancer-specific mortality. Furthermore, this observed reduction in mortality was independent of the use of statins or acetylsalicyclic acid. The reported median follow-up was 39 months (426).

5.3 Ovarian carcinoma

In several epidemiological studies, a clear correlation is found between the use of NSAID's and a decreased probability of developing ovarian carcinoma (427).
Valle et al. report that the NSAID's diclofenac and indomethacin exert an anti-proliferative effect in ovarian cancer in vitro and in vivo. The effects of NSAID's may be mediated, in part, by downregulation of the E2F1 protein (428).
In turn, Zerbini and colleagues report that combining NSAID treatment with NF-kB (Nuclear Factor kappa B) inhibitors results in enhanced apoptosis of ovarian cancer cells (429). The transcription factor NF-kB is suggested to play a pivotal rol in the regulation of the immune system. Hayden et al. expand further on the importance of NF-kappaB and the immune response (430).

As mentioned previously, propofol has been show to effectively inhibit proliferation and to induce apoptosis in human epithelial ovarian cancer cells (21).

Melhem and co-workers caution for administrating glucocorticosteroids on a standard basis to patients undergoing ovarian cancer surgery. Dexamethasone is often given as an anti-emetic during chemotherapy treatment. However, in their small (n = 19) study they demonstrated that administration of dexamethasone results in an increase of anti-apoptotic gene expression. This could subsequently result in a decrease in effectiveness of chemotherapeutic treatment (431).
By contrast, De Oliveira and colleagues were not able to find any relation between perioperative treatment with dexamethasone and ovarian cancer recurrence in their propensity-matched study. Their results therefore do not support avoiding low-dose perioperative (4-10 mg) dexamethasone for prevention of postoperative nausea, vomiting and pain in ovarian cancer surgery (432).

In case of breast cancer no potentially adverse effects of dexamethasone have been reported. Quite the opposite in fact, Bischofs and colleagues found an inhibitory effect of dexamethasone on breast cancer cell adhesion to endothelial cells. Thus, potentially decreasing the probability of developing metastases (200).

Rivard and colleagues claim that the use of patient controlled epidural anaesthesia after laparotomy for gynaecologic malignancy is associated with decreased intravenous and postoperative narcotic use and improved pain control without increasing complications or length of hospital stay. This claim is based on their retrospective study in which 112 women were studied. These patients were categorized into one of three groups: 1. Patient controlled analgesia (PCA); 2. PCA combined with transversus abdominis plane block (TAP); 3. Patient controlled epidural analgesia (PCEA). Apart from the abovementioned findings, a significant difference in the rate of intraoperative complications was reported, with lower rates in the PCEA group. In this study, bupivacaine was used as local anaesthetic (433).

Dong and co-workers studied the effects of epidural analgesia during ovarian surgery. Their study results show that that when general anaesthesia is combined with epidural analgesia, levels of tumour enhancing cytokines (IL 1β and IL 8) decrease, whilst those of tumour inhibiting cytokines (IL 10 and IFN γ) increase, as well as overall NK-cell activity. Therefore, they conclude that epidural analgesia enhances anti-tumour activity when administered perioperatively in ovarian surgical oncology (434).

Lin et al showed that general anaesthesia combined with epidural analgesia results in better 3- and 5-yr survival when compared to general anaesthesia combined with intravenous opioids (5. However, one has to point out that these findings are based on a retrospective study.

De Oliveira et al. demonstrated that the intraoperative use of neuraxial analgesia in ovarian surgical oncology is associated with an increase in disease-free interval, compared to administration of neuraxial analgesia in the postoperative phase only. This study was performed in patients undergoing primary cytoreductive surgery (436).

Elias reports that addition of epidural analgesia in patients undergoing primary cytoreductive surgery for stage III epithelial ovarian cancer is associated with a lower overall rate of cancer recurrence compared with general anaesthesia alone. Longer median disease-free survival was associated with more than 48 hours of epidural use, compared

with fewer than 48 hours. Finally, the use of desflurane was also associated wih lower overall rate of ovarian cancer recurrence compared with sevoflurane (437).

Capmas, on the other hand, was not able to find an association between epidural analgesia and better survival in cytoreductive ovarian cancer surgery. However, there appeared to be a trend in disease-free interval favouring epidural analgesia (438).
In their propensity-matched study, Lacassie et al. were also unable to find any beneficial effects of epidural analgesia on overall survival or time of cancer recurrence in patients undergoing ovarian cancer debulking surgery (439).

Hotujec et al. have studied the efficacy of transversus abdominis plane block (TAP) on 24-hour postoperative opioid use after robotic surgery for gynaecologic cancer. In their prospective trial, 64 patients with a gynaecologic malignancy were randomized into two groups. The first group received preoperatively a unilateral TAP block to the side of the assistant port via ultrasound guidance, comprised of 0.25% bupivacaine 30 ml with 3 mcg/ml epinephrine. The second group received a TAP block comprised of 30 ml saline. Opioid use measured. Results showed no significant differences in 24-hour postoperative opioid use in both groups. The authors therefore conclude that TAP block is safe and feasible in this patient population, but TAP block does not significantly decrease opioid use. However, it is not mentioned why TAP block was performed unilaterally instead of bilaterally. The exact type of surgery is also not mentioned (440).

As reported earlier in the case of S-ketamine, stimulation of beta-adrenergic receptors (as occurs during surgical stress) has the potential to enhance tumour growth in ovarian carcinoma (441). Fortunately, these tumour-enhancing properties prove fully reversible by beta-blockade.

Finally, Carus et al. conclude that a neutrophil index comprising elevated baseline neutrophils and absence of neutropenia was able to identify a high-risk group of ovarian cancer patients with only modest effect of chemotherapy (188).

In turn, Williams and colleagues confirm that an elevated neutrophil-to-lymphocyte ratio (NLR) before any form of treatment signals more aggressive disease and predicts poorer survival. Furthermore, CA125 was shown to directly correlate with neutrophils and inversely with lymphocytes (442). Cho, Thavaramara, Yesilyurt and Wang corroborate the prognostic significance of NLR in patients with ovarian cancer (443-446).

Yildirim et al. confirm the predictive value of the NLR and platelet-to-lymphocyte ratio (PLR) in the benign-malignant differentiation of adnexal masses. Based on this retrospective study, they report that both NLR and PLR appear to be useful parameters that can be applied together with Ca-125, due to the relatively high sensitivity values for the malign-benign differentiation of ovarian masses. Although the NLR and PLR show a lower specificity compared to Ca-125, their sensitivity appears higher. They conclude that, from the point of early detection of ovarian cancer, this may indeed prove very promising (447). In the case of early detection of cancer, a positive test result from a diagnostic test with a high sensitivity means that probability is low that a patient with cancer will be missed. Conversely, a positive test result from a diagnostic test with a 100% specificity means that all patients who test positive will prove to have cancer (448).

In their retrospective study, Kemal and colleagues show that NLR, PLR, and mean platelet volume (MPV) are significantly higher in epithelial ovarian cancer patients compared to healthy subjects. Furthermore, surgical tumour resection results in a significant decrease in MPV and NLR levels. Therefore, the authors conclude that MPV and NLR could be promising and easily available biomarkers for monitoring epithelial ovarian cancer patients (449).

However, Topcu and co-workers claim that NLR is an ineffective marker in predicting the malignant characteristics of a pelvic mass (450).

Sood et al. have studied the effects of stress-associated hormones norepinephrine, epinephrine, and cortisol on the (in vitro) invasive potential of ovarian cancer cells. The results of their study showed that stress levels of norepinephrine increased the *in vitro* invasiveness of ovarian cancer cells by 98%. Epinephrine also increased invasiveness, albeit

to a lesser extent than norepinephrine. Cortisol, on the other hand, did not significantly affect invasiveness. The β-adrenergic antagonist propranolol (1μmol/L) completely blocked the norepinephrine-induced increase in invasiveness. This indicates that stress hormones/catecholamines can enhance the invasive potential of ovarian cancer cells (451).

5.4 Cervical carcinoma

Only a few studies could be identified focussing on cervical cancer recurrence in relation to anaesthesia. In a retrospective cohort study 132 consecutive patients who were treated with brachytherapy were analysed. The use of neuraxial anaesthesia during the first brachytherapy appeared not to be associated with a reduced risk of local or systemic cancer recurrence, long-term mortality from tumour recurrence, or all-cause mortality compared with general anaesthesia (452).

Hong and Lim state that preemptive epidural analgesia is a reasonable approach for controlling perioperative immune function and preventing postoperative pain in patients undergoing cancer surgery. This statement is based on the results of their prospective, randomized, double blind trial in which forty women undergoing elective laparoscopic radical hysterectomy for cervical cancer were studied. Before induction of anaesthesia, these women were divided into two groups. One group received a mixture of lidocaine and morphine via an epidural catheter (preemptive group), the other group received the same volume of saline (control group) using sealed syringes. After peritoneal closure, the sealed syringes were administered in the reverse manner. All patients were then administered lidocaine plus morphine over a 72-hour period, using a patient-controlled epidural analgesia pump. In both groups, the interleukin-6 levels increased significantly after surgery. However, these elevations were significantly less pronounced in the preemptive group than in the control group. The opposite was observed with respect to interleukin-2 levels. The interleukin-2 level in both groups decreased significantly after surgery. Seventy-two hours after surgery, the interleukin-2 level returned to its baseline value in the preemptive group but not in the control group. The number of lymphocytes in both groups decreased

significantly after surgery. The pain scores at 6 and 12 hours after surgery in the preemptive group were also significantly lower than in the control group (453).

Although there is some evidence that perioperative intravenous administration of lidocaine might reduce the requirement of opioids, improve bowel function and shorten the length of hospital stay following abdominal surgery, Bryson and colleagues were unable to confirm these findings. In their randomized double-blind, placebo-controlled study, systemic intraoperative administration of lidocaine (as an intravenous bolus followed by an infusion) did not influence any of the above mentioned (454).

Grady et al., on the other hand, conclude that intraoperative infusion of lidocaine may improve postoperative pain levels and may shorten the time to return of bowel function after laparoscopic abdominal gynaecologic procedures. This conclusion is based on the results of their prospective, double-blind, placebo-controlled study, in which patients patients undergoing laparoscopic abdominal surgery were randomly assigned to two groups. Both groups received an intravenous lidocaine bolus of 1 mg/kg. The Lidocaine group received a continuous lidocaine infusion of 2 mg/kg/hr following induction of anaesthesia and discontinued 15 to 30 minutes before skin closure. In contrast, the Control group received a placebo infusion. Results showed that patients in the Lidocaine group had significantly lower postoperative day 3 pain scores and required less opioids. Furthermore, time interval from surgical start to return of first flatus was shorter in the Lidocaine group (455).

Chung et al. have studied the ON-Q pain management system in elective gynaecologic cancer patients undergoing lower midline laparotomy (456). As mentioned previously, the ON-Q® Pain Relief System is a non-narcotic elastomeric pump, placed by the surgeon intraoperatively, that automatically and continuously delivers a regulated flow of local anesthetic to a patient's surgical site or in close proximity to nerves, providing targeted pain relief for up to five days (Halyard).
In this prospective study, twenty gynaecologic cancer patients who underwent elective extended lower midline laparotomy were divided into two groups. One group received continuous wound perfusion with ropivacaine 0.5% during 72 hours into the supraperotoneal layer of the abdominal incision via the ON-Q pump. The other group

received intravenous patient-controlled analgesia using fentanyl and ondansetron. Postoeprative pain was assessed immediately and at 6, 24, 48, 72, and 96 hours after surgery. Postoperative pain scores at 24, 48, and 72 hours after surgery were lower in the ON-Q group than the IV PCA group. Therefore, the authors conclude that the ON-Q pain management system is a more effective approach than IV PCA for acute postoperative pain after extended lower midline laparotomy.

Zhang and colleagues claim that the preoperative Neutrophil-to-Lymphocyte ratio (NLR) is able to predict clinical outcome in patients with cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy (114). Their results show a significant association between a higher preoperative NLR and lower progression-free survival. They also studied the importance of platelet-lymphocyte ratio but were unable to find any predictive properties.
Mete Ural et al. report that in patients with endometrial cancer NLR is significantly higher compared with patients with normal endometrium (457).
Haruma and colleagues also state that pretreatment NLR is a predictor of poor prognosis in patients with endometrial cancer. Unfortunately, in this study, the NLR cut off point was not mentioned (458).

As reported earlier in the case of colon cancer (371), Seebacher and co-workers confirm the prognostic value of pretreatment plasma fibrinogen levels in patients treated for endometrial cancer. In their retriospective multi-centre study, low pre-treatment levels of fibrinogen (< 388.9 mg per 100 ml) were associated with better overall survival and disease-free survival (459).

Furthermore, Guzel and colleagues claim that pretreatment NLR also can be used as a biomarker of invasion in gestational trophoblastic disease (460).

Gungorduk et al. have studied the prognosctic significance of NLR (and PLR) in primary fallopian tube carcinoma and conclude that preoperative NLR is a prognostic factor. In this multicenter study, NLR > 2.7 was significantly associated with worse overall survival. Apart from a high NLR, advanced stage, suboptimal surgery and staging type were also

associated with worse outcome. In addition, patients with primary fallopian tube carcinoma who underwent bilateral pelvic and para-aortic lymphadenectomy had longer overall survival (461).

6. Skin/ soft tissue and muscle malignancies

Relatively few study results are available focussing on surgical oncology of skin, soft tissue and muscle malignancies.

As far as traceable, 3 studies focussed on controlling pain. Two studies showed that addition of S-ketamine to the pain medication not only results in decreased opioid consumption but also in better pain management, compared to treatment with morphine only in orthopaedic malignancies (462,463).

Weinbroum's study demonstrated that postoperative epidural analgesia results in better pain management than intravenous morphine by PCA-technique in patients undergoing surgery for orthopaedic malignancies (464).

Interestingly, a larger retrospective study on melanoma excision showed that the use of volatile anaesthetics as part of general anaesthesia was associated with lower survival when compared to the use of local anaesthetics (29).

Cata and colleagues claim in their paper that no studies could be identified reporting that regional anaesthesia and analgesia have a beneficiary effect on survival after musculoskeletal cancer surgery (465).

Gottschalk et al. report that, based on their retrospective analysis, a trend towards a better cumulative survival rate was demonstrated for patients with malignant melanoma undergoing inguinal lymph-node dissection under spinal anaesthesia, compared with general anaesthesia (466).

Based on their meta-analysis, Zhang and co-workers were unable to find any statistically significant chemoprotective effects of NSAID's on non-melanoma skin cancer (NMSC) (467).

Muranushi and colleagues, on the other hand, have conducted a systematic review based on published epidemiological studies and investitagetd whether use of aspirin and other NSAID's reduces the risk of cutaneous squamous cell carcinoma (SCC). Their results show a significantly reduced risk of SCC among users of non-aspirin NSAID's and among users of any NSAID's compared with non-users. Among aspirin users, a reduced risk was also observed, though with borderline statistical significance. Based on these findings, the authors conclude that NSAID's collectively have the potential to prevent the development of cutaneous SCC (468).
Reinau et al. report comparable results and conclude that patients predisposed to non-melanoma skin cancer might benefit from chemoprevention with NSAID's (469).

Hua and co-workers have studied the expression of COX-2 in squamous cell carcinoma and keratoacanthoma, and state that the positive expression rate of COX-2 is associated with the malignant degree of the tumour. Furthermore, they state that it may also help differentiate squamous cell carcinoma from keratoacanthoma (470).

As mentioned previously in the case of prostate and breast cancer, the absence of chemoprotective effects of NSAID's on NMSC could possibly be attributed to the fact that NMSC, including basal cell carcinoma and squamous cell carcinoma, is regarded as a cancer with a relatively low to medium malignancy grade. These types of cancer are often associated with a lower NLR, compared with more aggressive cancers. As in the case of breast cancer, the inflammatory grade has been shown to be a determinant factor in the success of (anti-tumour, anti-inflammatory) treatment. Accordingly, in patients with breast cancer and a high preoperative NLR (≥ 4), the use of NSAID's was associated with a reduction of the relative risk of cancer recurrence and mortality by more than 50%, compared to patients with a NLR < 4. In other words, breast cancer patients with a high NLR, a higher inflammatory grade and probably more aggressive cancer, profited most of the anti-inflammatory treatment with NSAID's (92). A cancer patient with a lower NLR may therefore benefit less from anti-inflammatory treatment than a cancer patient with a higher NLR.

Cananzi and Di Giacomo report that NLR is prognostic in patients treated for metastatic melanoma, either with ipilimumab or surgery (471,472). These findings are in accordance with the study results published by Jensen and co-workers, stating that neutrophil infiltration in primary melanoma cells is independently associated with poor prognosis (473).

Szkandera et al. claim that the derived NLR predicts poor clinical outcome in patients with soft tissue sarcoma. This claim is based on the results of their retrospective study, in which the pre-operative derived NLR was investigated in relation to disease-free survival and overall survival. Patients with a dNLR $\geq$ 2.39 had a significantly decreased disease-free and overall survival (474).

As mentioned previously in the case of S-ketamine, gastric and breast cancer, the use of beta-blockers also appears to be associated with a decreased risk of melanoma-related recurrence, metastasis and death (137).
Calvani and colleagues report that β3-adrenoreceptor (β3-AR) expression correlates with melanoma aggressiveness. Furthermore, the authors highlight that β3-AR expression is not only restricted to cancer cells, but it is also expressed in vivo in stromal, inflammatory and vascular cells of the melanoma microenvironment. In other words, norepinephrine promotes tumor microenvironment reactivity through β3-adrenoreceptors during melanoma progression (475).

Chang et al. report to have demonstrated that the β-blocker carvedilol has the ability to inhibit epidermal growth factor-induced malignant transformation of cells. This may suggest that carvedilol has chemopreventive activity against skin cancer. However, in models of established cancer, carvedilol had modest to no inhibitory effects on tumour growth of human cancer cells. Based on these results, the authors conclude that the β-blocker carvedilol may be repurposed for skin cancer chemoprevention, but may not be an effective treatment of established tumours (476).

In their review, Yang and Eubank expand further on the role of beta-adrenergic receptors and the potential use of β-blockers in adjuvant cancer therapy (477).

Finally, Fitzgerald, in his paper, provides us with an epidemiological overview of the use of beta-blockers, the role of norepinephrine and carcinogenesis (478).

In summary, evidence is mounting that increased norepinephrine/epinephrine release in the body, or increased numbers or sensitivity of norepinephrine/epinephrine receptors, is associated with increased occurrence of cancer in different organs. Adrenergic receptors are distributed over the entire body, and stimulation of these receptors modulates various intracellular processes. This stimulation may promote carcinogenesis through immune system dysfunction and pathological inflammation.
However, a few clinical studies show opposite results. In these studies, chronic beta-blocker use appears to be associated with an increased, instead of a decreased, risk of cancer. A possible explanation for these contradictory results could be the fact that certain patients already have and elevated endogenous (possibly genetic) norepinephrine signalling. For instance, patients with a genetically elevated norepinephrine tone are more likely to use antihypertensive medication, like beta-blokkers, and are also predisposed to to various types of cancer. The same holds true for, for instance, psychological stress. A distinction therefore should be made between the rapid and "phasic" adrenergic output, and the more steady, baseline adrenergic "tone". It is possible that the adverse effects of a longer-lasting elevated norepinephrine tone prevail over the beneficiary effects of beta-blockade.
Furthermore, there appear to be genetic differences in the norepinephrine component of the sympathetic nervous system within different persons.

A key component of the stress response involves the locus coeruleus and norepinephrine sympathetic system. The locus coeruleus (LC) is the major noradrenergic nucleus of the brain, giving rise to fibres innervating extensive areas throughout the neuraxis.
The other major neuroendocrine response to stress is via activation of the hypothalamic–pituitary–adrenal (HPA) axis, consisting of consequent release of corticotrophin releasing hormone and vasopressin, which stimulaye pituitary adrenocorticotropic hormone (ACTH) release. This leads to stimulation of glucocorticoid secretion by the adrenal cortex, which is essential for stress adaptation.

Chronic stress is associated with dysregulation of the HPA axis and the locus coeruleus and norepinephrine sympathetic system, with a consequent increase in the secretion of the hormone cortisol and elevated levels of norepinephrine and epinephrine.

7. Neuroendocrine malignancies

No study results could be identified dealing with neuroendocrine malignancies in relation to recurrence and anaesthesia.

8. Radiofrequency ablation in lung/liver/kidney/adrenal gland malignancies

Radiofrequency ablation (RFA) in oncology is a frequently used therapy in our Institute. Shah and co-workers provide an overview of its general features and outline its role in oncology (479).

Lai and colleagues focussed in their study on cancer recurrence after transcutaneous RFA in hepatocellular carcinoma. They differentiated between RFA under general anaesthesia and RFA combined with epidural analgesia. In this limited, retrospective study the type of anaesthesia appeared of no influence on overall survival. On the contrary, RFA under general anaesthesia was associated with a reduced risk of cancer recurrence compared to RFA with epidural analgesia. A satisfying explanation for this finding cannot be given (480).
In case of RFA of pulmonary tumours too, no differences could be detected with respect to anaesthetic technique and the effectiveness of treatment and/or the risk of complications (481).

Piccioni et al. have studied the use of thoracic paravertebral block as the sole anaesthetic in percutaneous hepatic radiofrequency ablation and conclude that this block produces satisfactory unilateral anaesthesia and minor adverse effects (482).

Meanwhile, Gazzera and colleagues report that although thoracic paravertebral blockade was achieved successfully in all the patients undergoing conscious percutaneous thermal ablation of liver tumours, 33% of these patients reported medium to severe pain and intravenous sedation was required (483).

Tohme and colleagues performed a retrospective study in patients with unresectable colorectal cancer undergoing hepatic radioembolization, and examined whether the Neutrophil-to-Lymphocyte ratio (NLR) predicts survival following this treatment. Their results show a median NLR of 4.6. Furthermore, a high NLR (≥ 5) was clearly associated with worse survival. Therefore, the authors conclude that NLR is a simple and novel biomarker for prediction of survival after radioembolization for metastatic colorectal cancer (484).

9. Trans-arterial chemo-embolization of the liver (TACE)

For some time, TACE procedures are being performed in a select group of patients in the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital. Most of these patients have been diagnosed with (solitary) liver metastases from colorectal carcinoma. The aim of this procedure is to obliterate the metastasis by trans-arterial embolization using the chemotherapeutic drug irinotecan.

Previous experience in our hospital revealed that our “standard” anaesthetic practice was not fully effective in preventing and/or treating the physical complaints related to this procedure. Our usual anaesthetic support, consisting of thoracic epidural analgesia (using a fractionated initial bolus of 50 mg of bupivacaine in combination with 25 mcg of sufentanil, followed by a continuous administration of a 0,05% bupivacaine and 0,02% morphine solution via a pump with an infusion rate of up to 20 ml/hour) in combination with intravenous propofol sedation, could not prevent patients from experiencing acute severe pain (NRS 10) in the epigastric area radiating into the back, shortly after the procedure had ended. Profound perspiration, severe nausea and vomiting accompanied this pain.

Strikingly, neither pain, nausea, or vomiting could be influenced by administering an extra bolus of epidural bupivacaine and/or intravenous S-ketamine and anti-emetics.

An extensive literature search revealed only one publication focussing on this issue (485). This publication underlines the complaints following this procedure as described above, and several recommendations are provided.

Interestingly, Wei and colleagues claim that the neutrophil-to-lymphocyte ratio (NLR) is a good predictor of survival in patients with hepatocellular carcinoma undergoing TACE combined with Sorafenib. In their study, high NLR proved to be an independent factor associated with worse survival (486).

10. Chemosaturation

Chemosaturation represents a new technique by which higher doses of chemotherapeutics can be delivered to cancer sites in the liver, allegedly more safely than by intra-hepatic artery perfusion. Its advantages are reported to be less invasive for the patient and, in case of cancer recurrence, the procedure can be repeated.
Basically, the procedure consists of three steps:

1. Isolation of hepatic venous outflow;
2. Catheter-directed saturation of the hepatic artery with very high doses of melphalan. "Embolizing" branches of the artery to prevent the chemotherapeutic from leaking into the arteries that supply other organs;
3. Filtration of the blood in the liver, which is shunted out and the put back in the body through the jugular vein.

For a more comprehensive overview on this procedure we refer to the articles published by Deneve and Uzgare (487,488).

We could only find one study focussing on the anaesthetic considerations regarding this procedure. The authors state that this procedure can be associated with transient but significant hemodynamic and metabolic perturbations. Therefore, they recommend administration of general anaesthesia, rather than sedation, for this procedure (489).
Our experience with this technique is limited, but we share the same hemodynamic and metabolic findings. In nearly all cases, high doses of norepinephrine are needed to maintain blood pressure. Since profound anticoagulation is needed, we perform this procedure under general anaesthesia without epidural analgesia. Until now, no further study results have been published focussing on the implications of this procedure in relation to type of anaesthesia, anaesthetics used and cancer recurrence.

II Recommendations

Recent research in the treatment of cancer shows a trend towards tracing and attacking tumour specific DNA mutations. On this basis, one in fact ought to discard the existence of organ specific cancers, and consequently their organ specific treatment, and focus on the treatment of each cancer as a unique entity. This development will hopefully lead to a situation in which increasingly more types of cancer will be classified as a chronic disease. In spite of this development, surgery will undoubtedly hold its leading part in the treatment of (solid) cancer.
For the purpose of clarity, we still have used the traditional classification of organ specific cancers in this compendium.

It may be obvious that results obtained from, for instance, animal research cannot directly be extrapolated to humans. Although there is clearly lack of prospective, randomized studies, and available study results are relatively scarce and frequently based on experimental, animal and/or retrospective studies, we do believe that disregarding this information could prove non-prudential on the longer term. As stated by Tavare and colleagues, there is an urgent need to determine the most appropriate anaesthetic strategy for surgical oncology to ensure that long-term survival is maximized, by using the most optimal anaesthetic techniques (490).
Fodale and co-workers point out that current data support the use of intravenous anaesthetics, like propofol, for its anti-tumoural protective effects by inhibiting cyclooxygenase 2 and prostaglandin E2 in cancer cells and stimulation of immunity; restriction in the use of volatile anaesthetics; restriction in the use of opioids (suppression of humoral and cellular immunity, and promotion of angiogenesis and development of metastases); use of neuraxial/locoregional anaesthesia. However, they caution that these findings must be interpreted cautiously (491).
In their paper, Das and colleagues indorse that perioperative care has a definite role in cancer survival and suggest modifying their current practice (492). Kaye cum suis, based on their evidence-based review, stress that clinical anaesthesiologists should be aware of the fact that immune responses from all components of the immune system appear to be

suppressed by anaesthetics and analgesics. These factors should therefore be considered in the application of technique, especially in cancer surgery (493).

Divatia and Ambulkar state that perioperative care has a definitive role in cancer-free survival and suggest modifying our current practice. This statement is based on literature review (494).

Consequently and in contrast to for instance Heaney et al. (495), Xuan et al. (496), Cakmakkaya et al. (497), and the recently published Consensus statement from the BJA Workshop on Cancer and Anaesthesia (498), we take the view that it is defendable, even in this still early stage, to incorporate some acquired study results to a certain level into daily practice, awaiting further findings.
If, at a later moment in time, certain recommendations prove to be of no or limited value to human patients, they can be adjusted or even completely deleted. This in fact comprises the essence of this compendium. Increasing knowledge of the effects of anaesthesia on surgical oncology will automatically result in expansion and adaption of this compendium.

In our opinion, simply stating that current research data are insufficient to indicate a change in clinical practice does not sound very sophisticated. The fact is that by doing so, one is forced to conclude that administering anaesthesia to, for instance, orthopaedic patients does not differ from administering anaesthesia to cancer patients. The fact that surgical cancer patients are more susceptible to the potentially deleterious effects of surgery hardly needs further elaboration. Applying the same yardsticks to all surgical patients shows little understanding of the impact of surgery on the human body.
Selecting the most appropriate technique in order to maximize patient comfort without unnecessarily burdening the patient should be our goal.

As described previously, surgery has a profound impact on the human body. Tissue damage caused by surgery ensues that various processes take place. This so-called surgical stress response results in an inflammatory reaction and ultimately in suppression of immunity. As expected, this suppression of immunity appears to be dose-dependent. The larger the surgically induced tissue damage, the more profound the inflammatory reaction and hence

more pronounced and longer lasting the suppression of immunity. Based on these premises, attenuating this surgical inflammatory stress response is one of the principal goals in anaesthesia. It is obvious that in the absence of anaesthesia, tissue damage caused by major surgery would inevitably result in the patient's death. To prevent this, administering anaesthesia with adequate perioperative analgesia is a condition sine qua non. Historically, opioids play a key role in restraining surgical stress. Although there is ample evidence that opioids exert a favourable effect on restraining the inflammatory stress response caused by the surgical procedure, evidence is growing that opioids also may exert unfavourable effects through immunomodulation.

Apart from the fact that pain and surgery appear to play a role in suppressing immunity, and consequently may be of influence on the oncologic process, there are several indications that the anaesthetics and pharmaceuticals administered during surgery can be of influence on tumour progression and cancer recurrence by interfering with various processes. Therefore, awaiting further evidence, we strongly believe that consumption of opioids should be limited, if possible. Needless to state, this limitation should never be at the expense of analgesic quality. Should this be the case, the adverse effects of the surgical inflammatory stress response will clearly prevail over the adverse effects caused by the treatment with opioids. Especially in surgical oncology, anaesthesia should focus on maximal reduction of surgical inflammatory stress with minimal impact on immunity and autonomous defence mechanisms. As inflammation is claimed by many to play a central role in tumour growth and metastasis, perhaps that through the use of certain anaesthetics the anaesthesiologist will even be able to fight cancer in a proactive manner.

II.1 With respect to surgical oncology of the head, throat and neck we have derived the following recommendations:

- General anaesthesia combined with adequate perioperative analgesia, with the aim to reduce the need for opioids, if possible.

- In extended surgery, intravenous administration of S-ketamine in analgesic doses can be considered next to administration of intravenous opioids, partly to reduce the need for opioids, partly to reduce the development of hyperalgesia and chronic pain However, as mentioned previously, there is strong evidence that the use of S-ketamine results in a decrease of the number of NK-cells with an associated reduction of autonomic defence mechanisms. Furthermore, S-ketamine has been shown to have beta-adrenergic stimulating properties and an evident correlation has been found between stimulation of the beta-adrenergic system and increased chance of developing metastases (134-138). Fortunately, the tumour-enhancing effects of S-ketamine could largely be undone by administering beta-blockade. One could therefore consider administering beta-blockade to surgical patients treated with S-ketamine, to neutralize it's potentially tumour promoting effects.
  Clearly, further studies are needed on this topic.

- Superficial cervical plexus blockade in unilateral surgery. Attention should be given to the location of needle insertion: obviously, it would be wise to insert the needle at a safe distance from the tumour to prevent local tumour spread. Based on previous study results, one could advocate the use of ropivacaine, rather than bupivacaine, because of its tumour inhibiting properties (44-46).

- Co-medication, using paracetamol and NSAID's such as diclofenac. In view of recent findings, it may be wise to withhold diclofenac in patients with a history of heart disease. Unless its use is contraindicated, we would advise to administer diclofenac at the end of surgery.

- With respect to the technique of general anaesthesia, there is some evidence that the use of volatile anaesthetics on their own may exhibit adverse oncologic effects. In anticipation of further study results, we would therefore advise to combine the use of volatile anaesthetics with intravenous propofol. At this time, we use intravenous propofol as a basis and regulate the depth of anaesthesia with a volatile anaesthetic like desflurane or sevoflurane. We use this strategy partly because of cost savings aspects. The use of a volatile anaesthetic in a low-flow setting is obviously far more cost saving than the use of intravenous propofol in case of prolonged surgery.

- Since neuraxial blockades are not possible for this type of surgery, one could theoretically expect beneficiary effects of simultaneous intravenous administration of lidocaine. Partly because of its opioid reducing effects, partly because of the anti-tumour properties of local anaesthetics (of the amide-type). Unfortunately, no study results have been published at this stage that back-up these assumptions. Further study results have to be awaited.

- As far as fluid administration is concerned, administration of balanced solutions, like for instance Ringers lactate, may have some beneficiary effects on attenuating the inflammatory stress response. Furthermore, there is some evidence that the use of balanced solutions results in less alteration of plasmatic electrolytes, acid-base equilibrium and kidney function.

II.2 In case of intra-thoracic tumours:

- In case of thoracotomy, we advise general anaesthesia combined with thoracic epidural analgesia. In our opinion, the benefits of adequate epidural analgesia outweigh the risk of potential complications. This holds only true if the anaesthesiologist has ample experience and inserts epidural catheters on a regular basis. Especially the insertion of high thoracic epidural catheters is a skill that has to be acquired and maintained by frequent performance. Our experience shows that in case of a high thoracic epidural, adding an opioid to the local anaesthetic, more frequently leads to side effects caused by the opioid, such as nausea, vomiting and itching. Therefore, we replace the opioid by clonidine. The most frequently used mixture in our department consists of bupivacaine (50 ml of a 0,5% solution in 500 ml saline 0,9%) to which 300 micrograms clonidine is added, instead of the usual 10 mg of morphine. This mixture is then infused at a rate of 16-20 ml/hour using an electrical syringe pump. We have deliberately chosen for a lower concentration of the local anaesthetic in favour of a higher volume, in order to achieve proper expansion of the block.

- As far as (diagnostic) thoracoscopy is concerned, we recommend unilateral paravertebral blockade combined with general anaesthesia. To our opinion, administration of merely a long acting local anaesthetic of the amide type, like ropivacaine, suffices to reduce the need for opioids adequately. However, recent reports suggest that the addition of clonidine to the local anaesthetic results in an even more intense block.

- As in the case of surgery to the head, throat and neck, we support the idea of combining intravenous propofol with volatile anaesthetics. Propofol as a basis and desflurane or sevoflurane to regulate the depth of anaesthesia.

- Co-medication with paracetamol and diclofenac (in the absence of contra-indications for the use of NSAID’s and a history of heart disease) is once more indicated. All the

more so, in case the patient requires treatment for concomitant ipsilateral post-thoracotomy shoulder pain.

- In case neuraxial blockade is contra-indicated or technically impossible, perioperative supplementary analgesia with intravenous S-ketamine seems a reasonable alternative. Again, combining S-ketamine with beta blockade to minimize its potentially adverse effects should be considered

- As mentioned previously, administration of balanced solutions may have some beneficiary effects on attenuating the inflammatory stress response and preserving electrolytes, acid-base equilibrium and kidney function.

II.3 In case of breast cancer:

- Especially in the case of breast cancer surgery, it appears to be advisable to reduce the use of opioids as much as possible.

- In case of bilateral mastectomy, we recommend general anaesthesia (volatile and intravenous) combined with high thoracic epidural analgesia. The restrictions mentioned for intra-thoracic tumours apply here as well: using lower concentrations of the local anaesthetic in a higher volume, and replacing the opioid with clonidine.

- If, for whatever reason, neuraxial blockade is impossible, supplementary treatment with S-ketamine once again may be an alternative. Our experience shows that in patients undergoing bilateral mastectomy side effects attributable to the use of S-ketamine are more frequently reported. These effects consist primarily of psychological complaints such as hallucinations. Combining S-ketamine with beta-blockade for reasons previously mentioned should once more be considered.

- In case unilateral mastectomy or wide local excision of the breast is performed, local infiltration of the breast is advised as preferred technique for analgesia in order to decrease opioid use (499). A dose of 40 ml of ropivacaine 0.5% results in sufficient analgesia without toxic side effects. We believe this is also the best analgesic technique in case of bilateral wide local excision of the breast. The field block can then be performed bilaterally, using up to a total of 60 ml of ropivacaine 0.5%.

- Patients undergoing unilateral mastectomy followed by immediate breast reconstruction represent a different category. Immediate reconstruction of the breast implies that layers of muscle tissue have to be exposed, resulting in more extensive surgery and hence greater stress response. In our experience, field blockade alone reduces opioid consumption inadequately in case of breast reconstruction. A favourable alternative would be a (unilateral) paravertebral blockade, as mentioned in the case of thoracoscopy. To which extent paravertebral blockade prevails over field blockade in case of mastectomy and direct reconstruction of the breast is a

matter of discussion in our department and is currently being investigated. Evidence so far suggests that ropivacaine is the local anaesthetic of choice for paravertebral blockades.

- The same previously mentioned recommendations apply for type of general anaesthesia and co-medication with paracetamol and diclofenac. Especially in case of breast cancer surgery additional treatment with diclofenac appears to be more than reasonable.

- Standard administration of dexamethasone 4 mg can be considered for patients undergoing breast surgery. Partly for its anti-emetic effect, but also because of its potentially inhibitory effect on the spreading of breast cancer cells, and hence reduced potential to metastasize.

- The recently introduced paravertebral lamina technique may hold a future role in breast cancer surgery. Further study results on its effectiveness have to be awaited.

- The same applies for treatment with intravenous lidocaine.

- As mentioned previously, administration of balanced solutions may have some beneficiary effects on attenuating the inflammatory stress response and preserving electrolytes, acid-base equilibrium and kidney function.

II.4 Based on the published study results on intra-abdominal and intra-pelvic surgical oncology the following general recommendations can be postulated:

- In case of laparoscopic surgery, general anaesthesia with opioid reduction appears to be the best choice. In this setting, ultrasound-guided Transverse Abdominal Plane blockade (TAP) is frequently used (500,501). Apart from its analgesic effects, a significant reduction of bladder spasms has been reported in laparoscopic surgery of the bladder and/or prostate. There is some evidence that ropivacaine is the local anaesthetic of choice for TAP in laparoscopic surgical oncology (44,45).

- In case of laparotomy, we recommend general anaesthesia combined with epidural analgesia. As mentioned previously, the administration of a higher volume of local anaesthetics is required in order to obtain sufficient expansion of the analgesic block. In contrast to high thoracic epidurals, neuraxially administered opioids in the middle and low thoracic area, are tolerated better and fewer side effects are reported. Therefore, we add a relatively small dose of morphine to the epidural mix in order to achieve a more intense sensory blockade. In the event of known morphine intolerance, morphine can be replaced by clonidine as described previously.
  Once more, it must be stressed that intraoperative volume resuscitation, in the presence of an epidural, should focus on goal-directed euvolemia in order not to impede the healing of a potential anastomosis (353).

  In case epidural analgesia is contraindicated or (technically) not possible, the administration of S-ketamine can be considered. Once more, it must be emphasised that S-ketamine has been shown to stimulate the beta-adrenergic system with possible subsequent adverse oncologic effects. Simultaneous beta-blockade should therefore be considered.

- For laparoscopy as well as laparotomy, the same recommendations apply for the type of general anaesthesia and co-medication with paracetamol and diclofenac. It has to be mentioned however, that the use of diclofenac may be associated with a greater risk for anastomotic leak in case of anastomosis of the ileum and proximal colon. To

what extent the beneficiary anti-tumour effects of diclofenac outweigh the greater risk for anastomotic leak has not (yet) been studied. Especially not in conjunction with the simultaneous use of epidural analgesia.

In case of anastomosis of the proximal colon or the ileum, the use of NSAID's in conjuction with thoracic epidural analgesia should be evaluated on an individual basis. In case of a high preoperative NLR, it appears to be advisable to initiate treatment with NSAID's 24 hours postoperatively. In case of a low NLR, and anastomosis of the ileum, the use of NSAID's remains arguable. As far as colorectal surgery is concerned, in our opinion, the beneficiary effects of diclofenac definitely outweigh the potentially deleterious effects on the integrity of the anastomosis. This is all the more so when epidural anaesthesia is being administered simultaneously.

- As mentioned previously, administration of balanced solutions may have some beneficiary effects on attenuating the inflammatory stress response and preserving electrolytes, acid-base equilibrium and kidney function.

II.5 When considering surgery of the vulva, soft tissue malignancies and surgery of the extremities, the same recommendations can be followed principally.

In case of less extended surgery, spinal anaesthesia is preferred. This on the basis of faster patient recovery, a decreased chance of side effects but most of all because of the earlier described potential tumour inhibiting effects of local anaesthetics (of the amide type). In this understanding, a future role may lie ahead for the intravenous use of lidocaine.

II.6 For radiofrequency ablation in lung, liver, kidney and adrenal gland we use (partly for logistic reasons) epidural analgesia combined with intravenous propofol sedation when necessary.

II.7 Since very little is known in relation to anaesthetic support in trans-arterial chemo-embolization of the liver (TACE), we follow the recommendations postulated by Giammaria Fiorentini et al (485):

- Ample pre-hydration before and during insertion of the thoracic epidural catheter in a monitored setting. Obviously, the patient's cardiac condition will determine the degree of pre-hydration. Needless to say, a urinary catheter has to be placed.

- As mentioned previously, administration of balanced solutions may have some beneficiary effects on attenuating the inflammatory stress response and preserving plasmatic electrolytes, acid-base equilibrium and kidney function.

- Administration of ranitidine 50 mg intravenously, for gastric protection.

- Administration of granisetron 1 mg and dexamethasone 8 mg intravenously, for maximal prevention of nausea and vomiting.

- Administration of cefazolin 1000 mg intravenously for antibiotic prophylaxis.

- Administration of our standard epidural medication (initial bolus of bupivacaine 0,5% 10 ml followed by a mix of bupivacaine 0,05% with the addition of morphine 10 mg at a rate of 20 ml/hour). At the time of the initial bolus 25 mcg of sufentanil is also administered epidurally.

  For reasons not yet understood, patients undergoing this procedure appear to require opioids in order to attenuate the stress response. Treatment with merely local anaesthetics appears to control the complaints insufficiently. The level of stress response is obviously determined by the exact location of injection, the amount of Irinotecan injected and its injection rate.

- Administration of lidocaine intra-arterially by the radiologist, just at the beginning of the procedure.

II.8 Chemosaturation

We could only find one study focussing on the anaesthetic considerations regarding this procedure (489). The authors state that this procedure can be associated with transient but significant hemodynamic and metabolic perturbations. Therefore, they recommend administration of general anaesthesia, rather than sedation, for this procedure.

Our experience with this technique is limited, but we share the same hemodynamic and metabolic findings. In nearly all cases, high doses of norepinephrine are needed to maintain blood pressure. Since profound anticoagulation is needed, we perform this procedure under general anaesthesia without epidural analgesia. Until now, no further study results have been published focussing on the implications of this procedure in relation to type of anaesthesia, anaesthetics used and cancer recurrence.

III Epilogue

Major developments take place in the field of Medicine. Our own Institute has recently launched a campaign in which a promise has been made that within considerable time 90% of all cancers will be classified as a chronic disease. The traditional treatment of (solid) cancer, consisting of treatment with chemotherapeutics, radiation therapy and/or surgical excision, will increasingly focus on mutations in cancer DNA, making specific and individual treatment available. Till then, surgical excision of the tumour will remain an important pillar in the treatment of cancer.

It is a well-known fact that surgery has a profound impact on the body. Although surgery is performed to "cure" the body, a considerable prize has to be paid for this cure. The integrity of the body is affected and consequently numerous processes are triggered to ensure that homeostasis is maintained. Simply put, although the human body is a highly complex entity, the way the body is able to cope with various threats is limited. To a certain degree, all threats, varying from an infection to major (surgical) trauma, are dealt with by an inflammatory stress response. This inflammatory response triggers several processes, and these processes eventually lead to a catabolic state in which immunity and defence mechanisms are adversely affected. It may be obvious that immunomodulation may have a direct impact on tumour growth and progression.

Furthermore, evidence is growing that this common inflammatory stress response plays a key role in the perioperative period by influencing tumour growth, tumour progression and metastasis. An increasing number of studies suggest that the neutrophil-to-lymphocyte ratio (NLR) may be used as an inexpensive biomarker that reflects the individual degree of inflammation. Furthermore, the NLR also appears to be useful as a prognostic tool for several types of cancer and their treatment. Apart from cancer, NLR also appears to be related to mortality in different disease groups, such as pulmonary emboli and acute coronary syndrome. A recent study even suggests that NLR is an independent indicator of short- and long-term mortality in critically ill patients (502).

All these findings support the hypothesis that the inflammatory stress response is a common pathway through which the body deals with different kinds of threats affecting the integrity of the body.

In addition, there are some indications that even symptomatic treatment of the (surgical) inflammatory stress response may have beneficial effects in patients undergoing cancer surgery. For instance, anti-inflammatory treatment with NSAID's and treatment with beta-blockers has been shown to be able to affect tumour progression.

Recent developments in anaesthesia have been spectacular. Nowadays, anaesthesia is administered worldwide and is reported extremely safe. It has evolved in such a way that most of the patient's complaints after surgery can be attributed to the impact of surgery and not to anaesthesia itself. Opposite to what the general public believes, most patients experience and tolerate anaesthesia well.

Although we have come a long way, a long path still has to be followed. Evidence is growing that anaesthesia may have an impact on tumour evolution. Although anaesthesia has never been shown to induce cancer, recent study results reveal that certain anaesthetics and anaesthesia techniques may have an effect on cancer growth and its potency to metastasize. In that view, anaesthesia should not merely focus on minimizing (surgical) stress response, but also on preserving immunity and the body's own autonomous defence mechanisms. We trust that by modulating the inflammatory response, the anaesthesiologist will be able to contribute to the successful surgical treatment of cancer.

Growing insight into the role of inflammation and the NLR as a biomarker will hopefully enable us to modify the inflammatory environment perioperatively.
We hope that this compendium, even in this still rudimentary form, will provide some guidelines in choosing the most appropriate anaesthetics and anaesthesia techniques for the administration of anaesthesia in surgical oncology.

IV Literature

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