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Anaesthesia in Surgical Oncology

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– Ovid, Metamorphoses, VIII, 18 –

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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

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), and decreased survival through suppression of tumour-specific CD8+ T cells (9).

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 (10-13). 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 (11).

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 (14). It has been demonstrated that patients with lower NK-cell activity have a higher incidence of malignancies (13). 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 (13). Animal research has shown that this reduced NK-cell activity can result in more rapid tumour growth (15).
Page GG et al. demonstrated that postoperative pain solely is able to act as a mediator for tumour enhancing effects of surgery in rats (16).

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 (17).

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.

Angka et al. expand on the significance of dysfunctional NK-cells in the perioperative period (18).

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. (11)).

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 (19). On the other hand, other studies reported propofol to have protective effects by inhibiting invasion of human colonic cancer cells (20,21).

These contrary results made Zhang study the effects of propofol on gallbladder carcinoma. He found that the use of propofol was associated with an (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 (22).

Song et al. report that propofol exhibits anti-cancer effects by promoting apoptosis (23). Su and colleagues confirm that propofol can effectively inhibit proliferation and induce apoptosis of human epithelial ovarian cancer cells (24). Zhang et al. demonstrate that propofol exhibits anti-tumour effects by inhibiting growth of human hepatocellular cancer cells (25).

Wang and colleagues report that propofol suppresses both the proliferation and invasion of gastric cancer cells via downregulation of microRNA-221 expression. Furthermore, propofol is also reported to suppress proliferation and invasion of pancreatic cancer cells by upregulation of microRNA-133a expression (26,27).

Yang's group claims that propofol suppresses the accumulation of hypoxia-inducible factor 1α and tumour aggressiveness in non-small cell lung cancer (28).

Wu et al. conclude that propofol is able to inhibit lipopolysaccharide-induced pro-inflammatory cytokines and pro-inflammatory enzymes expression in microglial cells through inhibition of N-methyl-D-aspartate (NMDA) receptors (29).

Wang's group provides an overview of the cancer modulating properties of propofol and the responsible mechanisms (30).

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 attenuation of the surgical inflammatory stress response (31).

Interestingly, Ammar and Mahmoud report that, compared to sevoflurane, propofol reduces renal injury after elective open abdominal aortic aneurysm repair. In this prospective, randomized study postoperative urinary concentrations of all measured kidney specific proteins and serum pro-inflammatory cytokines were significantly lower in the propofol group compared with the sevoflurane group. In other words, propofol appears to have a more protective effect on renal ischaemia/reperusion injury following open aortic aneurysm repair compared with sevoflurane anaesthesia (32).

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 (33), 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 (34,35). 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 (36).

Miyata et al. have studied the effects of general anaesthesia with isoflurane following propofol induction on natural killer cell cytotoxic 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 (37).

Zhang and Shao demonstrate that isoflurane promotes non-small cell lung cancer proliferation, migration and invasion by activating the Akt-mTOR signaling pathway (38).

In turn, Wei and colleagues report that 5% sevoflurane induces apoptosis of A549 lung alveolar epithelial cells, which results in decreased cell viability, increased apoptotic bodies, impaired DNA integrality and increased levels of caspase 3/7 (39).

Zheng's group has compared the effects of isoflurane, sevoflurane and desflurane on neuroinflammation and cognitive function in mice. Based on their results, the authors conclude that surgery under desflurane anaesthesia results in reduced neuroinflammation and cognitive impairment compared with surgery under isoflurane anaesthesia (40).

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 (41). By contrast, Lindholm's study revealed no increased incidence of new malignant disease in patients anaesthetized with sevoflurane. In this study, nor the duration of sevoflurane anaesthesia, nor its depth appeared to be of influence (42).

Wigmore et al. have performed a retrospective trial in which the effects of volatile and intravenous anaesthesia were compared with respect to long-term survival in patients undergoing cancer surgery. Their results demonstrate an association between type of anaesthesia delivered and survival. Volatile anaesthesia was associated with worse survival (3 year) compared to intravenous anaesthesia (43).

Based on their in vitro study, Ecimovic and colleagues report that sevoflurane increases proliferation, migration and invasion in oestrogen receptor-positive breast cancer cells (ER(+)), and proliferation and migration, but not invasion, in oestrogen receptor-negative

breast cancer cells (ER(-)). However, the observed effect size was small and not dose-dependent (44).

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 chemo resistance. Exposure to propofol, on the other hand, resulted in partial reduction of cancer cell malignant activities (45).

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 (46).

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 (47). 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 (48).

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 (1231).

Nonetheless, Marana and co-workers report that desflurane and sevoflurane produce a different stress response in the setting of laparoscopic surgery. Based on the results of 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 anaesthesia. However, both vapours did not influence the plasmatic levels of Interleukin-6 (IL-6), CRP and glucose (49). The clinical significance of these findings remains unclear.

With respect to the analgesic requirements following anaesthesia with volatile anaesthetics, Fassoulaki and colleagues report that opioid consumption and pain 24 hours postoperatively do not differ among postoperative patients undergoing abdominal hysterectomy under sevoflurane, desflurane or propofol anaesthesia (50).

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 (51). 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 (52).

Local anaesthetics

Local anaesthetics, like lidocaine and ropivacaine, appear to inhibit proliferation as well as growth of cancer cells in vitro (53). Lidocaine showed a distinct anti-tumour effect in an in vitro study in human tongue carcinoma (54). Other studies have confirmed these findings (55, 56). Strikingly, Piegeler demonstrated that only local anaesthetics of the amide type display these inhibiting properties, in contrast to local anaesthetics of the ester type (57).

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 loco regional techniques are considered in surgical oncology (58). These “anti-inflammatory” effects are believed to be independent of sodium channel inhibition.
By contrast, Lucchinetti and co-workers claim that lidocaine, ropivacaine and bupivacaine reduce mesenchymal stem cell proliferation. Furthermore, multiple transcriptional programs related to cell differentiation, tumour genesis, and metastasis were negatively affected by ropivacaine (59).
Chang et al. confirm that lidocaine and bupivacaine induce apoptosis in human breast cancer cells and human thyroid cancer cells (60,61).

Xuan’s group concludes that bupivacaine has direct “anti-cancer” properties (reduction of cell viability and inhibition of cellular proliferation and migration) through the activation of intrinsic and extrinsic apoptotic pathways in ovarian cancer. With respect to prostate cancer, bupivacaine displayed these anti-cancer properties only through the intrinsic pathway (62).

Ramirez et al. report that clinically relevant concentrations of lidocaine enhance the in vitro function of NK-cells via the release of lytic granules (63). Furthermore, they claim that lidocaine stimulates the function of natural killer cells in different experimental settings. Therefore, the authors suggest that lidocaine might be used perioperatively to minimize the impact of surgery on NK cells (64).

Chamaraux-Tran and Piegeler support the potential importance of intravenous lidocaine as part of the perioperative anaesthesia regimen in reducing the risk of cancer recurrence or progression in patients undergoing cancer surgery (65).

Le Gac et al. demonstrate that lidocaine and ropivacaine induce profound modifications in gene expression profiles of tumour cells, which result in a cytostatic effect and induction of apoptosis (66).

By contrast, Bundscherer and co-workers claim that only high concentrations of ropivacaine or bupivacaine reveal anti-proliferative potency in colon and pancreatic cancer cells in vitro (67).

Gonzalez and Altermatt have performed a systematic meta-analysis in which the effects of intravenous lidocaine on pain and postoperative recovery time were investigated. Based on their results, they conclude that the use of intravenous perioperative lidocaine probably results in a clinically irrelevant difference in pain and hospital stay. But, it might probably prevent postoperative nausea and vomiting (68).

With respect to the management of chronic pain and based on the results of their literature review, Yousefshahi et al. conclude that both intravenous lidocaine and lidocaine patch are effective and safe for the treatment of several chronic or neuropathic pain syndromes. Therefore, the use of lidocaine during surgery could prevent the development of some chronic post-surgical pain syndromes (69).

In their paper, Votta-Velis and colleagues address the relation between inflammation, cancer and amide-linked local anaesthetics (70).

Hahnenkamp and colleagues report that epidural analgesia has the potential to improve patients' outcome after major surgical procedures by reducing postoperative morbidity and duration of recovery. Possible benefits include the attenuation of cardiac complications, an earlier return of gastrointestinal function associated with an increase in patients' comfort overall, decreased incidence of pulmonary dysfunction, beneficial effects on the coagulation system and a reduction in the inflammatory response. However, the underlying mechanisms remain unclear. It is postulated that local anaesthetics, reabsorbed from the epidural space, seem to contribute to these effects. Therefore, the authors conclude that in patients not able or willing to receive epidural analgesia, systemic administration of local anaesthetics may be considered to be a new therapeutic approach for the prevention of postoperative complications by modulation of the peri-operative period (71). Obviously, further study results are required to confirm this hypothesis.

Picardi et al. demonstrate that local anaesthetics affect the function of human neutrophils, independently of sodium-channel blockade, and by doing so exhibit significant immunomodulatory effects (72).

Opioids

Opioids administered both perioperatively and chronically display evident effects on both cellular and humoral immunity (73,74). These effects include decreased NK-cell activity, production of immunity stimulating cytokines, phagocytic activity and production of antibodies (75). 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 (76). A breast cancer study in mice showed that administration of morphine resulted in an increase in angiogenesis and more rapid tumour growth (17). Markedly, this morphine effect could be undone by administering celecoxib without abolishing its analgesic effects (77).

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 (78). 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 pre-emptive mechanism (79).

Grace and co-workers demonstrate that using morphine for treatment of pain caused by abdominal surgery may in fact prolong the pain felt by the patient. The mechanism responsible for this paradoxal response lies in the fact that morphine and surgery together cause excitation of the nervous system glial cells and this excitation consequently leads to

extra pain signals being sent out to nerves in surrounding regions. Morphine also has been shown to bind to a receptor in brain glial cells, the so-called opioid-induced toll-like receptor 4 (TLR4). Stimulation of this receptor initiates pro-inflammatory cytokine and chemokine release that have anti-analgesic effects against the classical opioid-receptor-mediated analgesia (80).

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.

Xie's group demonstrates that morphine alters the circulating proteolytic profile in mice, thus altering the tumour microenvironment, which in turn displays functional consequences on cellular migration and invasion of cancer cells (81).
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 (82).
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 (83).

However, Owusu –Agyemang and colleagues have retrospectively investigated the effects of perioperative opioid consumption on survival in adolescents undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy, and their results suggest that opioid consumption is not (significantly) associated with recurrence-free or overall survival (84).

Grandhi and co-workers have performed a systemativc review in which the relationship between morphine use and angiogenesis and metastasis in in vitro models was investigated. They conclude that morphine has a potential causal relationship with angiogenesis and metastasis. This is likely due to multiple etiologies, including immunosuppression, pro-inflammation, and pro-angiogenesis (85).

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 (86). These findings are supported by previous study (87). 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 (88,89). 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 stromal 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 (90-92).

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 (93).

Janku and co-workers report that treatment with methylnaltrexone, a peripherally acting μ-opioid receptor (MOR) (FDA-approved for treatment of opioid-induced constipation) is associated with increased survival in patients with advanced cancer. Based on this finding, the authors conclude that MOR can play a role in cancer progression and that targeting these receptors with methylnaltrexone warrants further investigation in cancer therapy (94).

With respect to epithelial-mesenchymal transition (EMT), Kim et al.’s study results suggest that dexamethasone has inhibitory effects on cell migration and invasion by suppressing EMT of colon cancer cell lines in hypoxic condition (95).

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) (96).

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 (97).

For further information regarding inflammation and cancer we refer to the paper by Coussens and Werb (98).

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 (99-100).
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.

For a more detailed overview on the relation between surgery, inflammation and cancer we refer to the paper by Roxburgh and colleagues (101).

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 (102-104).

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 (105). 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 (106).

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 (107,108).

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 (109). 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 (110-112). 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 (113,114). Johannesdottir demonstrated a preventive effect in certain skin tumours, including melanoma and basal cell carcinoma (115). Singh confirmed that diclofenac is able to induce apoptosis and differentiation in human acute myeloid leukaemia cells (116). Finally, Mayorek demonstrated comparable anti-tumour effects in pancreatic carcinoma cells (117).
Amanullah et al. expand further on the possible mechanisms by which diclofenac induces apoptosis and exerts its anti-carcinogenic properties (118).

Based on emerging evidence, Pantziarka and colleagues even suggest that diclofenac might play an important role in the treatment of cancer, particularly in combination with other agents (119).

Paul-Clark et al. demonstrate that a hydrogen sulphide-releasing NSAID displays profound chemopreventive effects in a mouse model of intestinal tumourigenesis (120).

Will’s group reports that local release of diclofenac increases survival rate in a murine model of recurrent oral carcinoma. Therefore, local drug release of anti-inflammatory agents should be investigated as a therapeutic option in the prevention of tumour recurrence in oral squamous carcinoma (121).

Kumar and co-workers show that nanoformulated naproxen (and other NSAIDs) displays unusual anticancer activity. In fact, nanoformulated naproxen displayed the highest anti-leukaemia activity, and was more than twice that of doxorubicin, which is a standard anticancer drug. Nanosizing is performed to improve the solubility and bioavailability of drugs (122).

Intini et al. describe the synthesis, biological effects, and mechanisms of action of new platinum(II) derivatives containing one or two non-steroidal anti-inflammatory diclofenac ligands. These compouds are reported to have potent antiproliferative properties and act as cancer cell selective cytotoxic agents exhibiting activity in cisplatin resistant and COX-2 positive tumour cell lines (123).

Aran and colleagues report that parainflammation, a low grade of inflammation, is widely prevalent in human cancer, especially in cancer types commonly harbouring p53 mutations. Parainflammation may thus be a driver for p53 mutagenesis and a guide for cancer prevention by NSAID treatment (124).

Umar, Suthar, Santilli and Todoric expand further on the mechanisms of NSAIDS in cancer prevention and treatment (125-128).

However, it has to be mentioned that one should be very cautious when administering diclofenac to patients with cardiovascular disease. Ghosh and colleagues report that diclofenac may induce cardiotoxicity by a reactive oxygen species (ROS) mechanism involving mitochondrial and proteasome dysfunction (129).
Based on the results of their nested case-control study, Thöne and co-workers conclude that the use of diclofenac and ibuprofen, the most frequently used NSAIDs, is associated with a 40 to 50% increased relative risk of acute myocardial infarction, even for low cumulative NSAID amounts (130).

Bryant et al. also state that NSAIDs might have a direct negative influence on muscle repair after acute strain injury (in mice). Therefore, they advise to be extra cautious in subscribing NSAIDs to patients with progressive loss mass such as the elderly or patients with cancer or AIDS (131).

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, which 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 (132).

As discussed previously, 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 (133-134).

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 (135).

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 (136). 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 (137). 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 (138). 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 (139).

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 (140-164). 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 (165).

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 (166). 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.

However, it must be mentioned that Sanchez-Covarrubias and colleagues caution for a possible drug-drug interaction between morphine and the non-steroidal anti-inflammatory drug diclofenac. Based on their study results, they conclude that both peripheral inflammatory pain and diclofenac treatment alone results in decreased morphine uptake in the brain (through increased P-glycoprotein (P-gp) efflux activity). Morphine analgesia was significantly reduced in animals pre-treated with diclofenac, as compared to animals administered diclofenac and morphine concurrently (167). The implication of these findings remains unclear.

Finally, Hooijmans et al. have performed a systematic review and meta-analysis on the effect of treatment with analgesics on metastasis in experimental animal models. Their results show that treatment with analgesics significantly decreased the number and risk of metastasis. Furthermore, this effect appeared mainly to be the consequence of the efficacy of NSAIDs. There was no evidence, indicating that treatment with any analgesics increases the occurrence of metastases (168).

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 (169-181). 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, a correlation has been found between stimulation of the beta-adrenergic system and increased possibility of cancer recurrence and/or development of metastases (182-186). 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.

Cheong and Salamon expand further on the role of β-adrenergic receptors in hypoxia and their effects on glucose metabolism.
Cheong et al. state that β-adrenergic receptors play a fundamental rol in sensing hypoxia (187).
Finally, Rains and co-workers report that β-adrenergic receptors (β-ARs) are expressed across diverse cancers, most strongly in melanoma. Other cancers that revealed relatively higher levels of β-ARs were oesophagus, pancreas, kidney and lung cancers (188).

Salamon and colleagues describe the Warburg effect, which states that the main source of energy for cancer cells is not aerobic respiration, but glycolysis, even in normoxia. The shift from aerobic respiration to anaerobic metabolism is governed by mutually counteracting enzymes, pyruvate dehydrogenase and pyruvate dehydrogenase kinase. Anaerobic metabolism of cancer cells has been shown to promote cell proliferation, local tissue immunosuppression, resistance to hypoxic conditions, and metatstatic processes. By switching back to oxidative metabolism, these effects may be reversed, for instance by using pyruvate dehydrogenase kinase inhibitors. Therefore, the authors conclude that patients suffering from ischaemic conditions might benefit from these effects. Additionally, the β-blockers often used in these patients appear to improve cancer-specific survival, and non-selective β-blockers have been shown to promote glucose oxidation. For this reason, the authors suggest that there might be a link (189).

In addition to this, Malsy et al. report that ketamine and S-ketamine significantly inhibit proliferation and apoptosis in pancreatic cancer cells (190).
Luggya's groups states that a low dose of ketamine attenuates early serum Interleukin-6 levels (IL-6) following surgery with a reduced 24 hour increase. However, this difference proved not statistically significant (191).

Interestingly, although a benefit is described of ketamine as an adjuvant analgesic in cancer pain in different open-label studies, Jonkman and colleagues were unable to detect any effect on pain relief or reduction of opioid consumption in their meta-analysis. Nevertheless, they conclude that there is still insufficient evidence to state with certainty that ketamine is not effective in cancer pain (192).

Based on the results of their randomized, controlled trial, Fan and co-workers conclude that S-ketamine rapidly relieves acute depression and suicidal ideation in newly diagnosed cancer patients (193).

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 (194). Yücel et al on the other hand were not able to confirm this correlation in their study. Therefore, they conclude that mild hypothermia does not affect tumour recurrence or mortality (195).

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 (196) Amato and Pescatori, on the other hand, found evidence for some correlation in their Cochrane Database Review (197), whilst Kekre's results show that duration of storage of red blood cells is of no influence on cancer recurrence or overall survival (198). 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 allogeneic blood transfusion and systemic tumour progression and/or survival outcomes in their retrospective study on patients undergoing radical prostatectomy (199).

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 (200).

By contrast, Bergamin et al. observed a survival trend favouring a liberal blood transfusion strategy in oncologic patients with septic shock when compared with a restrictive strategy. In this randomized, double-blinded, controlled trial, liberal strategy was defined as haemoglobin threshold < 9 g/dL (< 5,59 mmol/L), while restrictive strategy was defined as haemoglobin threshold < 7 g/dL (< 4,34 mmol/L). At 90 days after randomization, mortality rate in the liberal group was significantly lower than in the restrictive group (201).

Poveda and Nasciemento claim that hypothermia is associated with increased length of stay in the Post-Anaesthetic Care Unit (PACU), but not with the need for blood transfusion during the intra- and postoperative periods in patients undergoing gastrointestinal cancer surgery (202).

As mentioned previously in the case of S-ketamine, there is growing evidence that stress and β-adrenergic receptor stimulation may have an effect on tumour development and progression.

Yang 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 (203).

Choi and colleagues claim that there is evidence that beta-blocker use can be associated with prolonged survival of cancer patients, especially patients with early-stage cancer treated primarily with surgery. In this meta-analysis, beta-blocker use was associated with improved overall survival and disease-free survival (204).

Based on the results of their retrospective study, Hwa and co-workers report that in patients with multiple myeloma, beta-blocker use is associated with a reduced risk of disease-specific death and overall mortality, in comparison to non-beta-blocker use or no use of cardiac drugs (205).

Coelho's group has performed a review in which the effects of beta-blockers on cancer cell proliferation were investigated. Based on the results, the authors conclude that the reviewed studies show strong evidence that beta-adrenergic receptor activation (through several intracellular mechanisms) modulates tumour cell proliferation. Thus suggesting that beta-blockers can represent a feasible therapeutic approach to antagonize beta-adrenergic response or that beta-blockers have a protective effect per se (206).

For a more comprehensive review of the impact of (adrenergic) stress on cancer evolution we refer to the papers published by Meier, Eng and Krizanova (207-209).

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 (210).

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 (211).

Interestingly, Pedersen and co-workers report that voluntary exercise suppresses tumour growth through epinephrine- and Interleukin-6-dependent NK cell mobilization. In this study, tumour-bearing mice randomized to voluntary wheel running showed over 60% reduction in tumour incidence and growth. NK cell infiltration was significantly increased in tumours from running mice, whereas depletion of NK cells enhanced tumour growth and blunted the beneficial effects of exersise. Furthermore, NK cells were mobilized by epinephrine, and blockade of β-adrenergic signalling blunted training-dependent tumour inhibition (212).

He et al. expand further on the potential anticancer effect of β-blockers and the genetic variations involved in the interindividual difference (213).

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 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 (214).

Although S-ketamine has the disadvantage of stimulating β-adrenergic receptors, as described previously, it appears that ketamine has a beneficiary effect on the treatment of depressions. Iglewicz et al. have studied this effect and conclude that ketamine may be as safe, effective, and rapid treatment for clinical depression in patients receiving hospice care (215). Since this conclusion is based on a retrospective study, randomized, blinded, and controlled trials are required to substantiate these findings.

Finally, Braun and colleagues claim that S-ketamine (at millimolar concentrations) induces apoptosis via the mitochondrial pathway in human lymphocytes and neuronal cells (216).

1. Head, throat and neck 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 (217) and is increasingly used in case of an unexpected difficult airway (218).

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 (219).
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 (72-85) and even to potentially increase cancer recurrence (74-86,220). 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 (116-177,221).

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 (222-225). Based on previous study results, one could advocate the use of ropivacaine, rather than bupivacaine, because of its more pronounced tumour inhibiting properties (57,58).

3. Co-medication with paracetamol and COX-2 inhibitors (107-109). Keeping in mind the diversity of diclofenac's working mechanism, this NSAID may be preferable to other NSAIDs (118,226). However, it should be mentioned that based on recent findings the use of diclofenac in patients with cardiovascular disease and/or congestive heart failure may be contraindicated (129,131). Furthermore, Parzefall et al. state that NSAIDs should be administered with caution after laryngopharyngectomy due of an increased risk of pharyngocutaneous fistula development after NSAID use (227).
   Bhoyar et al. report that intraoperative diclofenac use during maxillofacial cancer surgery has an opioid sparing effect (228).
   Hiller et al. demonstrate that standard dosing of the COX-2 inhibitor celecoxib reduces, albeit slightly, perioperative cyclooxygenase activity during intracavity cancer surgery. Furthermore, it also lowers postoperative pain scores (229).

Unfortunately, only a few studies 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 (230).

Cata et al. have retrospectively investigated the effects of intraoperative opioids use on recurrence after laryngeal squamous cell carcinoma surgery. Their results demonstrate a weak association between the use intraoperative of opioids and recurrence of laryngeal carcinoma (p= 0.02) (231).

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 (232). 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 (233).

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-signalling 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 (234).

Klatka’s group concludes that COX-2 inhibition can be regarded as an immunotherapy-enhancing tool in patients with laryngeal cancer. This conclusion is based on the results of their study in which COX-2 inhibition resulted in an enhanced proliferation of NK cells (235).

Zhang and colleagues demonstrate that hydrogen sulphide, being one of the main causes of halitosis in the oral cavity, promotes oral cancer cell proliferation through activation of the COX-2/AKT/ERK1/2 axis (in a dose-dependent manner) (236).

This emphasizes the relationship between inflammation and oral squamous cell cancer.

Lee and co-workers have investigated the effect of celecoxib on survival in patients with mobile tongue cancer and report that, when combined with chemotherapy, celecoxib may have a beneficial effect on the survival of this group of patients. Patients who received celecoxib combined with chemotherapy had significantly higher disease-specific survival compared to patients who were treated with chemotherapy without celecoxib. However, recurrence-free survival was not different between the two groups (237).

Tang and colleagues have performed a meta-analysis in which the association between NSAIDs and aspirin use and the risk of head and neck cancers (HNC) was investigated. Their results indicate a modest reduction in HNC risk with ibuprofen and long-term aspirin use. However, overall use of NSAIDs was not associated with a reduced risk of HNC (238).

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 (155). Duzlu and colleagues confirm the importance of NLR in larynx carcinoma. In their retrospective study, a high NLR was significantly higher in patients with larynx carcinoma compared to the control group (239).

Charles and co-workers support the prognostic properties of NLR in patients with oropharyngeal and non-oropharyngeal mucosal squamous cell carcinoma. NLR > 5.0 was significantly associated with shorter overall survival (240).
Liao’s group confirms that a high pretreatment NLR acts as an independent poor prognostic factor in patients with nasopharyngeal carcinoma. In this retrospective analysis, a high NLR was defined as NLR ≥ 3.6 (241).

Based on their retrospective analysis, Wang and colleagues report that markers of systemic and local inflammation, especially PLR and tumour infiltrating lymphocytes (TILs) density, are reliable prognostic factors for overall and recurrence-free survival in patients with laryngeal squamous cell carcinoma (242).

Salim et al. claim that NLR is an independent prognostic factor for overall survival in patients wih recurrent or metastatic head and neck squamous cell cancer. In their retrospective study a high NLR (> 2.93) was significantly associated with worse overall survival (243).

Bobdey and co-workers also conclude that higher pretreatment NLR and monocyte levels are independent predictors of poor prognosis for patients with oral cavity cancer. In their retrospective study, NLR (> 2.38) and monocyte count (≥ 500/mm3) were significantly associated with worse overall survival (244).

Ozturk's group reports that preoperative NLR, and PLR, may be used to predict local recurrence in early-stage tongue cancer (245).

Kawakita et al. have conducted a multi-institutional retrospective cohort study in which the impact of haematological inflammatory markers on clinical outcome in patients with salivary duct carcinoma was evaluated. Their results show that the modified Glasgow Prognostic Score (mGPS), high C-reactive protein (≥ 0.39 mg/dl), and high NLR (≥ 2.5) were significantly associated with worse overall survival. In contrast to high mGPS and high CRP, high NLR was inconsistently associated with worse progression-free survival. Finally, there was no significant association of PLR with survival (246).
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.

Haddad and colleagues confirm that NLR is prognostic for mortality in patients with locally advanced head and neck cancer. They have studied 46 patients with primary mucosal

squamous cell carcinoma treated with chemoradiotherapy with a follow-up of 12 months. Results showed that pre-treatment NLR ≥ 5.0 was significantly associated with worse overall survival (247).

Moon et al. report comparable results. In their prospective study pre-chemoradiotherapy high NLR was an independent predictor of progression-free survival, cancer-specific survival, and overall survival in patients with head and neck squamous cell carcinoma (248).

Fu and co-workers have retrospectively investigated the association between cancer-specific survival, overall survival, and the preoperative NLR in patients with advanced laryngeal squamous cell carcinoma undergoing total laryngectomy. Patients with an NLR ≥ 2.59 showed a significantly lower cancer-specific survival (CSS) and overall survival (OS) than patients with an NLR < 2.59. Therefore, the authors conclude that the NLR may be used as an independent prognostic marker for CSS and OS in patients with advanced laryngeal squamous cell carcinoma undergoing total laryngectomy (249).

Chen et al., on the other hand, claim that preoperative PLR is superior to NLR as an independent indicator in predicting disease-free and overall survival in patients undergoing oral cancer resection for oral squamous cell carcinoma (250).

It has to be mentioned, however, that, according to Al and colleagues, cigarette smoking may influence NLR. Based on their cross sectional study, they conclude that heavy smokers exhibit dyslipidaemia with increased RBC count, total leucocyte count with specific increase in neutrophils (251).

Interestingly, Maruyama's group reports that NLR is predictive of wound healing failure in microsurgical head and neck reconstruction. In their retrospective study, preoperative neutrophil ratio (< 64.9%), NLR (< 3.5), and PLR (< 160) were significantly associated with the rate of wound healing failure (252).

Katoumas et al. report that the NSAID sulindac displays anti-neoplastic effects on oral squamous cell carcinoma in vivo (253).

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 (254).

The same group has also conducted an observational cohort study of patients with UADT cancer. The results of this study show that aspirin and other NSAIDs presciptions after diagnosis are associated with reduced all-cause mortality in UADT cancer patients (255).

Becker and colleagues support the claim that the use of NSAID's is associated with a reduced risk of head and neck cancer. In their case-control analysis, regular use of ibuprofen was significantly associated with a decreased risk for head and neck cancer, especially for cancer of the larynx (256).

Sun and co-workers have retrospectively investigated the prognostic significance of various hematologic parameters in patients with nasopharyngeal carcinoma. Their results show that pretreatment NLR ≥ 2.7, and PLR ≥ 167.2, were significantly associated with shorter progression-free survival. Only PLR ≥ 163.4 was associated with poor overall survival (257).

By contrast, Chua et al. report that in patients with stage III/IVA/B nasopharyngeal carcinoma treated with chemo- and radiotherapy, high pretereatment NLR (≥ 3.0) is associated with advanced T-satus, N-status, overall stage, and high pretreatment Ebstein-Barr virus DNA titre. However, high NLR was not associated with overall survival, disease-free survival, distant metastasis-free survival, and locoregional recurrence-free survival (258).

Nakashima's group states that NLR is a potential biomarker for predicting the clinical response to 5-FU-based chemoradiotherapy and survival in oral squamous cell carcinoma

(OSCC) patients. In their retrospective study, an elevated NLR was significantly correlated with advanced stage and poor response to chemoradiotherapy. Furthermore, NLR and pathological response to chemoradiotherapy were significant prognostic factors for disease-free survival. Also, circulating IL-6 was found to correlate with NLR and C-reactive protein (259).

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 (260).
Wong and colleagues confirm the prognostic value of pretreatment NLR in patients with laryngeal squamous cell carcinoma (261).

In turn, Kim and co-workers claim that a high preoperative PLR is significantly associated with lateral lymph node metastasis in patients with papillary thyroid cancer (262).

Gong and colleagues support these findings in patients with papillary thyroid cancer. In their retrospective survey, preoperative NLR was closely related to the TNM stage of this type of cancer (263).
Ozmen at al. also have retrospectively studied the prognostic value of NLR in patients with differentiated thyroid cancer. Their results show that higher NLR (and PLR) is associated with higher levels of thyroglobulin, which indicates worse survival. Furthermore, the authors conclude that NLR may be superior to C-reactive protein (CRP) for predicting the occurrence of differentiated thyroid cancer (264).

Nakahira's group states that the combination of platelet count and NLR might be used as a useful predictor of survival in patients with hypopharyngeal squamous cell carcinoma (265).

Cho et al. report that NLR can discriminate between papillary thyroid cancer (PTC), poorly differentiated thyroid cancer (PDTC), and anaplastic thyroid cancer (ATC). In other words, the authors claim that the NLR may play a relevant role as a discriminating tool and may be considered as a new diagnostic criterion in discriminating as well as in selecting therapeutic approaches to the aggressive forms of thyroid cancer (266).

By contrast, Liu's group claims that an elevated NLR is not a reliable indicator of progressing differentiated thyroid cancer in patients with goiters. This claim is based on the results of their meta-analysis of 7 prospective cohort studies involving 7349 patients (267).

Huang and colleagues have studied the prognostic value of the pre-treatment 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 (268).

Valero and co-workers confirm that high pretreatment count of neutrophils and/or monocytes is independently related with worse prognosis in patients with head and neck cancer (269).

Turri-Zanoni's group reports that high pretreatment NLR and PLR are associated with poor prognosis in patients affected by epithelial advanced-stage primary sinonasal cancer (270).

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 (271).
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 (272).

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 (273).

Xie et al. conclude that stress hormones may affect oral cancer behaviour by influencing the tumour 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 benign 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 (274).

Chang and co-workers have performed a population-based cohort study comprising over 24.000 patients in which the effects of propranol use on cancer risk were examined. Their results show that patients with propranolol treatment exhibited significantly lower risks of cancer in head and neck, oesophagus, stomach, colon and prostate cancers. The authors conclude that these results support the proposition that propranolol can reduce the risk of head and neck, oesophagus, stomach, colon and prostate cancers (275).

Wei et al. demonstrate that the non-selective β-adrenergic receptor antagonist propranolol inhibits growth and induces apoptosis of thyroid cancer cells both in vitro and in vivo. The β1-specific antagonist atenolol lacked these effects. Furthermore, propranolol was able to amplify the cytotoxicity of vemurafenib and sensitize thyroid cancer cells to the cytotoxic effect of vemurafenib (276).

Pantziarka's group expands further on the anticancer effects of propranolol and states that these effects should be investigated, especially in combination with other agents (277).

Kim et al. have performed an observational study of 10.414 person-years of follow-up in which the use of β-blockers and other antihypertensive drugs on recurrence and mortaliy in head and neck cancer patients was investigated. Strikingly, their results showed that β-blocker use was significantly associated with poor cancer-specific mortality, competing mortality, and all-cause mortality in normotensive patients. Furthermore, calcium-channel blocker use was associated with with increased cancer recurrence in patients with head and neck squamous cell carcinoma (278).

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 analgesics 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 pre-emptive analgesic after head-neck cancer surgery (279).

Wang et al. have performed a prospective, randomized and placebo-controlled trial in which the effects of preemptive analgesia with parecoxib on plasma stress hormones and haemodynamics were studied in patients with thyroid carcinoma undergoing thyroidectomy. The results indicate that preemptive analgesia with parecoxib before anaesthesia and after surgery effectively reduces the levels of plasma stress hormones (norepinephrine, cortisol and blood glucose) and improves analgesic effects in surgical patients with thyroid carcinoma, without conspicuous impact on haemodynamics (280).

Yet, Patel and colleagues report that neither non-aspirin NSAIDs nor aspirin use is associated with a reduced risk of thyroid cancer. In their pooled prospective population-based study female sex and obesity were associated with an increased risk of thyroid cancer, wheras smoking and alcohol use were associated with a decreased risk of thyroid cancer (281).

Based on the results of their prospective, randomized trial, Bae and colleagues claim that ropivacaine instillation after robotic thyroid surgery reduces acute postoperative pain and analgesic requirements without adverse events (282).

Paek et al. have performed a prospective pilot study in which the level of postoperative surgical stress following robotic thyroidectomy was compared with the level of surgical stress after open thyroidectomy. Interestingly, no significant differences were observed between both groups with respect to IL-6 level, white blood count or CRP level. Only VAS score after open surgery was significantly higher than after robotic operation (283).

Ferrell and co-workers report that anaesthetic techniques have an effect on the morphoproteomic expression of head and neck squamous cell carcinoma. In their prospective, randomized study, exposure to sevoflurane (in combination with remifentanil) but not to propofol increased the expression of pro-oncogenic protein markers in head and neck squamous cell carcinoma (284).

Pintaric et al. have compared the efficacy of superficial cervical plexus block with combined deep and superficial cervical plexus blockade in patients undergoing minimally invasive parathyroidectomy. The results of this prospective, randomized comparison indicate that superficial blockade is a good alternative to combined block, with comparable results with respect to the onset of block, pain scores, opioid consumption and possible side effects (285).
El-Shmaa and El-Baradey report that dexmedetomidine (1 μg/kg as intravenous infusion) attenuates the hemodynamic stress response to laryngoscopy and endotracheal intubation more effectively compared with labetolol (0,25 mg/kg as intravenous infusion) without any

deleterious effects. Furthermore, dexmedetomidine also decreases the dose of propofol for induction of anaesthesia (286).

Long's group confirms that intraoperative use of dexmedetomidine reduces narcotic administration postoperatively in patients undergoing thyroidectomy (287).

Abd El-Rahman and El Sherif have prospectively investigated the effects of postoperative local wound instillation with ketamine following total thyroidectomy. Their results show that local wound instillation with ketamine provides superior postoperative analgesia with lower incidence of side effects compared to intramuscular ketamine and placebo in this group of patients (288).

Finally, Kainulainen et al. have investigated the effects of dexamethasone in head and neck cancer patients undergoing microvascular reconstruction. In their prospective, randomized, double-blinded study, patients treated with a total dose of 60 mg of dexamethasone during 3 days peri- and postoperatively had no benefit with respect to neck swelling, legth of intensive care unit and hospital stay, duration of intubation or tracheostomy, and delay to start of possible radiotherapy. On the contrary, these patients had more complications, especially infections (289). Apparently, prolonged treatment with higher doses of dexamethasone renders patients more prone for infections.

However, these findings conflict with the results of a recently published study, in which the effects of dexamethasone administration on postoperative infection in surgical patients was investigated. In this propensity-matched post hoc analysis, dexamethasone administration to high-risk non-cardiac surgical patients did not increase the risk of postoperative wound infection or other adverse events up to day 30. Therefore, dexamethasone administration appears to be safe in patients either with or without diabetes mellitus (290).

Schiegnitz and colleagues have prospectively determined the serum levels of pro-inflammatory cytokines in patients with oral premalignant lesion (OPL), oral squamous cell carcinoma, and healthy controls. The pro-inflammatory cytokines interleukin-6, interleukin-8 and soluble interleukin-2 receptor (sIL-2R) were significantly elevated in oral squamous

cell carcinoma (OSCC) patients compared to healthy controls and OPL patients. Furthermore, higher T-grade and positive lymph node involvement resulted in significantly higher IL-6 values. Higher IL-6 and sIL-2R serum values were significantly associated with lower survival rate compared to OSCC patients with low IL-6 and sIL-2R values. In conclusion, the authors state that IL-6, IL-8 and sIL-2R are strongly associated with OSCC oncogenesis, and that Il-6 and sIL-2R appear to be promising and potent biomarkers for evaluation the prognosis of patients with OSCC (291).

With respect to the surgical inflammatory stress response following selective neck dissection, Fan et al. conclude that endoscopic selective neck dissection provides lower inflammatory responses and surgical stress, thus reducing perioperative trauma and accelerating recovery, compared to open neck dissection. In this prospective study, endoscopic surgery resulted in significantly lower release of IL-6, IL-10, CRP and cortisol (292).

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.

Sun et al. report that dexamethasone can inhibit the growth and angiogenesis of residual Lewis lung carcinoma cells in mice subsequent to palliative surgery, partially through downregulation of hypoxia inducible factor 1α and vascular endothelial growth factor (293).

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 (294).
Moody and colleagues report that S-diclofenac inhibits the growth of non-small cell lung cancer (NSCLC) and reduces prostaglandin E2 (PGE2) levels (295).

Li et al. report that tumour interstitial fluid might provide better nutrition to the tumour than angiogenesis and that it could promote the development of malignant phenotypes of lung cancer independently of angiogenesis (296).

Based on the results of their meta-analysis, Hou et al. report that the combination of the selective COX-2 inhibitor celecoxib and chemotherapy appears to improve overall response rate as compared with chemotherapy alone in patients with advanced non-small cell lung cancer (297).

Ling and co-workers have prospectively investigated the effects of parecoxib combined with thoracic epidural analgesia on pain and the stress response after thoracotomy. They conclude that intravenous parecoxib in multimodal analgesia improves postoperative analgesia provided by thoracic epidural analgesia, relieves stress response even further, and may restrain the development of chronic pain (298).

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 (221).

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 (299,300).

However, Melamed and Shakhar demonstrate 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 (182,183). In this 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) (301). Remarkably, 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 pre-emptive effect (302).
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% (303).

Kosinski et al. have compared the analgesic efficacy of continuous thoracic epidural analgesia and percutaneous continuous paravertebral blockade in patients undergoing VATS lung lobectomy. Based on the results of their randomized, non-inferiority trial, they

conclude that postoperative pain following VATS lung resection is significant and requires the application of complex analgesic techniques. Furthermore, percutaneous continuous paravertebral blockade proved equally effective as thoracic epidural analgesia in providing analgesia in this group of patients (304).

Mercanoglu and colleagues have studied the effectiveness and side effects of intravenous or epidural use of morphine, bupivacaine or ropivacaine on post-thoracotomy pain management. The results of their randomized, double-blinded, prospective study revealed that morphine used via the epidural route was found more effective than via the intravenous route. Furthermore, morphine administered epidurally proved more effective in the late postoperative period, whilst the administration of morphine and bupivacaine together was more effective in the early period (305).

Shah's group concludes that intraoperative continuous epidural analgesia decreases post-anaesthesia care unit (PACU) length of stay as discharge criteria for patient-reported NRS pain scores are met earlier. This conclusion is based on the results of their retrospective chart review of thoracic, abdominal, and orthopaedic surgeries where an epidural catheter was placed prior to surgery (306).

Based on the results of their prospective and randomized study (in which the effects of two different anaesthesia methods on cellular immune function following resection of lung carcinoma were investigated) Chen et al. report that TIVA combined with epidural anaesthesia and analgesia interferes less with the immune system compard with TIVA alone (307).

Alexin and Khoronenko even claim that the use of thoracic epidural analgesia significantly decreases the frequency of postoperative atrial fibrillation in patients undergoing extended lung surgery (being most effective in patients undergoing lobectomy) (308).

Özbek and co-workers have investigated the added value of neuraxial analgesia in patients undergoing open lung resection. Compared to general anaesthesia, the combination of neuraxial analgesia with general anaesthesia resulted in lower incidences for acute

myocardial infarction, pulmonary complications, blood transfusion and mechanical ventilation. However, there was an increased incidence for thromboembolic events in the neuraxial group (309).
The latter is a remarkable finding since Hollmann et al. have shown that epidural analgesia prevents immediate postoperative hypercoagulability without affecting physiologic aggregation and coagulation processes (1030).

Ke and colleagues have performed a meta-analysis in which epidural anaesthesia was compared with general anaesthesia with respect to operating time and postoperative hospital stay time in patients undergoing video-assisted lung surgery. Their results suggest that epidural anaesthesia has more advantages than general anaesthesia with respect to operative time. Furthermore, epidural anaesthesia showed a favourable surgical outcome on postoperative hospital stay. Therefor, the authors conclude that epidural anaesthesia can save operating time and hospital stay time compared to general anaesthesia. However, in this meta-analysis epidural anaesthesia was not associated with fewer complications (310).

Dumans-Nizard et al. have performed a prospective, double-blind, placebo-controlled study in which the effects of epidurally administered levobupivacaine on remifentanil and propofol consumption were evaluated in patients undergoing thoracotomy. Their results show that the administration of levobupivacaine allows for a decrease by one-third of remifentanil requirement (311).
Surprisingly, Chan and colleagues report that levobupivacaine induces dissemination of lung cancer cells in vitro and in vivo. By contrast, other amide-type local anaesthetics, including ropivacaine, lidocaine and bupivacaine did not facilitate dissemination in their study (312).

Based on the results of their prospective, randomized study, Xu’s group claims that both combined general-epidural anaesthesia (CGEA) and total intravenous anaesthesia (TIVA) affect cellular immunity. However, general anaesthesia combined with thoracic epidural analgesia had a reduced effect on cellular immunity compared with TIVA. Furthermore, CGEA displayed improved postoperative analgesic effects. In other words, in patients undergoing thoracoscopic surgery for non-small cell lung cancer, thoracic epidural

analgesia combined with general anaesthesia attenuates the surgical stress response to a greater extent when compared with TIVA (313).

Also based on the results of a prospective, randomized study, Zawar and colleagues report that thoracic epidural analgesia decreases stress and inflammatory response to surgery and decreases hospital stay in patients undergoing off pump coronary artery bypass surgery (314).

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 anaesthetic 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 (315).

Ried et al. also compared the ON-Q catheter system with thoracic epidural analgesia in patients 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 (316).

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 resection 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 (317).

Miyazaki's group has conducted a randomized open control trial in which the effects of early postoperative administration of pregabalin on postoperative pain following lung cancer surgery were evaluated. Compared with epidural analgesia and non-steroidal anti-inflammatory drug use, pregabalin administration showed no beneficial effects for patients with NSCLC undergoing surgery. Both groups showed similar frequency of additional NSAID use, similar NRS for the intensity of ongoing pain, and similar frequency of neuropathic pain at any time until 3 months after surgery (318).

Tamura et al. have prospectively compared the analgesic effects of thoracic epidural analgesia with thoracic paravertebral blockade via the surgical field in patients undergoing thoracotomy. Their results showed that epidural blockade is superior to paravertebral blockade (inserted in the paravertebral space by the surgeon). Furthermore, the incidence of side-effects, like lower blood pressure, was similar in both groups (319). Obviously, any pre-emptive effect was absent in the paravertebral blockade group.

The same applies to the study performed by Khalil and co-workers. In their randomized, observer-blinded, controlled study lung cancer patients were randomly allocated to the serratus anterior plane block (SAPB) group, or the thoracic epidural analgesia (TEA) group. SAPB was performed before extubation and after wound closure with and injection of of 30 ml 0.25% levobupivacaine followed by continuous infusion of 5 ml/hour of 1.125%

levobupivacaine. In the TEA group, epidural catheters were inserted preoperatively, to be activated before extubation using a lower dose regimen compared to the SAPB group. Results showed comparable VAS scores and similar total dose of morphine consumed in both groups. Furthermore, mean arterial pressure was significantly decreased in the TEA group compared with the SAPB group (320). Pre-emptive effects were obviously abolished in this study design.

Yamauchi et al. have compared the analgesic effects of continuous paravertebral blockade using a thoracoscopic catheter-insertion technique with thoracic epidural analgesia. In this retrospective case-control study, patients who underwent thoracotomy with PVB were included. Prior to thoracotomy incision, a catheter for PVB was inserted percutaneously into the paravertebral space under thoracoscopic guidance. A matched-pair control group was selected from patients who underwent thoracotomy with thoracic epidural analgesia. Pain control and side effects were compared between groups. Results showed that pain scores on postoperative day 2 did not differ significantly between both groups. With respect to side effects, urinary retention occurred less frequently in patients with thoracic PVB (321).

Cata and colleagues have studied the effects of type of postoperative analgesia after surgery for non-small cell lung cancer on recurrence-free and overall survival. Results of this retrospective study showed that the type of postoperative analgesia (intravenous patient-controlled analgesia, patient-controlled epidural analgesia, and their combination) was not associated with better overall and recurrence-free survival (322).
Lee et al. also retrospectively investigated the effects of paravertebral blockade on cancer recurrence in patients following lung cancer surgery. Their results show that PVB is not associated with reduced cancer recurrence. However, PVB might have a beneficial effect on overall survival of patients with lung cancer (323).

With respect to paravertebral blockade, Hassan and Mahran state that the addition of dexmedetomidine to PVB with bupivacaine provides more effective analgesia with improvement in postoperative functions in patients undergoing thoracic surgery. This statement is based on the results of their prospective study in which addition of dexmedetomidine 1 µg/kg as a bolus and 0,2 µg/kg/hr by continuous infusion resulted in a

significant reduction of intra- and postoperative opioid consumption in the first 24 hours. Futhermore, VAS score during cough was reduced and postoperative pulmonary functions were improved (324).
However, in their propensity score-matched retrospective study, Cata's group reports that intraoperative use of dexmedetomidine is associated with decreased overall survival after lung cancer surgery. Obviously, we are in need of randomized controlled studies focusing on this subject (325).

Based on the results of their retrospective study in non-small cell lung cancer patients, Oh et al. report that the amount of opioid usage is not associated with recurrence or mortality (326).

Jones and Asteriou suggest a greater pro-inflammatory response in patients undergoing lung resection via thoracotomy compared with VATS (327,328). 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).

Oddly enough, Cata et al. report that immunity is not preserved in patients with non-small cell lung cancer (NSCL) after surgical resection by the use of epidural analgesia. This conclusion is based on their observational single-centre study, in which patients with NSCL cancer undergoing thoracotomy with epidural analgesia were studied. Although the percentage and function of natural killer cells was significantly decreased after surgery, the percentage of natural killer T cells, T helper cells, and cytotoxic T lymphocytes remained unchanged (329).

Xu and co-workers, on the other hand, report that surgical trauma can induce postoperative T-lymphocytes dysfunction in lung cancer patients through the programmed death-1 pathway. Furthermore, this dysfunction appears to correlate with the severity of surgical trauma. Apart from this dysfunction, the count of T-lymphocytes and natural killer cells was reduced after surgery with a significantly increased level of inflammatory cytokines and stress hormones (330).

Interestingly, Ju et al. have studied the effects of inhaled budesonide on respiratory 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 (331).

Based on the results of their prospective, randomized study, Potočnik's group reports that sevoflurane appears to display anti-inflammatory effects in patients undergoing open lung surgery with one-lung ventilation. Patients allocated to the sevoflurane group had significantly lower interleukin-6 and postoperative CRP levels compared with patients allocated to the propofol group. Pre- and postoperative procalcitonin was within the reference range in both groups (332).
Tian and colleagues have prospectively compared the effects of sevoflurane anaesthesia with propofol anaesthesia on the perioperative inflammatory response in patients undergoing lung cancer resection. Based on the results, the authors conclude that propofol anaesthesia, compared to sevoflurane anaesthesia, can significantly reduce the perioperative inflammatory response, shorten recovery time, protect pulmonary function, and reduce the prevalence rate of intraoperative adverse reactions (333).

As mentioned previously, Zhang and Shao demonstrate that isoflurane promotes non-small cell lung cancer proliferation, migration, and invasion by activating the Akt-mTOR signaling pathway (334).

Sen et al. have prospectively investigated the effects of pressure-controlled (PCV) and volume-controlled ventilation (VCV) on respiratory mechanics and systemic stress response in patients undergoing percutaneous nephrolithotomy. Results showed that when compared with VCV mode, PCV mode is associated with lower P-peak and P-plateau levels during both supine and prone positions, better postoperative oxygenation, lower blood cortisol levels during surgery in prone position and in the early postoperative period. Therefore, the

authors conclude that PCV mode might be more appropriate in prone position during anaesthesia (335).

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 (82).
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 (83).

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 (86).

Zylla and colleagues have retrospectively examined if long-term opioid requirement, independently of chronic pain, is associated 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 (336).
Wang et al. also retrospectively evaluated the effect of postoperative mu agonists on overall survival and disease-free survival in early stage NSCLC patients. Their results show that postoperative opioid usage was related to shorter overall survival and disease-free survival for patients with NSCLC undergoing surgery (337).

Kashiwagi and colleagues have compared the efficacy of ultrasound-guided thoracic paravertebral blockade (TPVB) with epidural analgesia in patients undergoing video-assisted thoracoscopic surgery (VATS). They claim that TPVB affects hemodynamics less than epidural analgesia. However, there was also less postoperative analgesic effect with TPVB than with epidural analgesia (338).

On the other hand and as mentioned previously, Kosinski's group states that continuous PVB is as effective as continuous thoracic epidural analgesia in providing analgesia in this group of patients (304).

Rao et al. state that ropivacaine wound infiltration might be a safe and effective fast-track approach for patients undergoing thoracotomy surgery. In their prospective, randomized, double blinded study, local wound infiltration with ropivacaine resulted in significantly lower pain scores, lower opioid consumption, shorter postoperative hospital stay, earlier ambulation, and higher patient satisfaction scores compared to local wound infiltration with placebo (339).

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 (57).

Wang's group demonstrates that amide-linked local anaesthetics induce apoptosis, and suppress invasion and migration of human non-small cell lung cancer cells (340).

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 (137).
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 (341). 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 (342).

Huang and colleagues, on their turn, claim that NLR in combination with enhanced contrast computed tomography is a valuable tool in detecting regional lymph node metastasis in patients with non-small cell lung cancer. The combination of enhanced contrast computed tomography with NLR (COCT-NLR) was reported to have a sensitivity of 70.6% and a specificity of 74.9% in predicting nodal involvement (343).

Cannon et al. state that pre-treatment 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 (344).

Based on their retrospective analysis, Bar-Ad and colleagues report that elevated pretreatment NLR is a potential biomarker to identify lung cancer patients with poor prognosis (345).

Diem's group claims that elevated pre-treatment NLR and PLR are associated with shorter overall survival, shorter progression free survival, and with lower response rates in patients with metastatic NSCLC treated with nivolumab (346).

Derman et al. conclude that high baseline and progressive increases in NLRs are associated with progressive disease, inferior overall survival and weight loss in NSCLC patients (347).

In turn, Käsmann and colleagues state that NLR predicts oucome in patients with limited disease small-cell lung cancer. In their study, NLR < 4 was an independent prognostic factor for improved survival and metastasis-free survival (348).

Lan et al. have conducted a single institutional cohort study in which the prognostic properties of NLR and PLR in NSCLC patients undergoing radical lung surgery were investigated. Their results show that both preoperative NLR and PLR were good prognostic factors for postoperative complications and overall survival in NSCLC patients undergoing surgery (349).
Deng and colleagues confirm the predictive value of pretreatment NLR in patients with small-cell lung cancer. In this retrospective study, NLR ≥ 2.65 was an independent risk factor for worse progression-free survival and overall survival (350).

By contrast, Jin's group claims that postoperative NLR and ΔNLR, but not preoperative NLR, act as independent prognostic factors of disease-free survival and overall survival in patients with stage I NSCLC undergoing complete resection (351).

Sanchez-Salcedo et al. report that in a lung cancer screening setting, the assessment of annual PLR change could help predict lung cancer development (352).

Han's group reports that PLR, but not NLR, is an independent prognostic factor in patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (353).

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 (354).

Lee et al. support the prognostic value of PLR in patients with NSCLC undergoing surgery. In this retrospective study, high PLR (≥ 180) was significantly associated with reduced rates of recurrence-free survival and overall survival. Although a higher preoperative inflammatory status was associated with decreased rates of survival, perioperative use of NSAIDs was not found to be an independent predictor of survival in this retrospective study (355).

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 (NSCLC) (356).

Tang and colleagues have investigated the prognostic performance of NLR in locally advanced NSCLC treated with endostar and concurrent chemoradiotherapy. Their results confirm that NLR and monocyte count independently predict overall survival in patients with stage III NSCLC treated by a combination of anti-angiogenic therapy and concurrent chemoradiotherapy. An elevated pre-treatment NLR and monocyte number were negatively associated with overall survival (357).

Giuliani and co-workers endorse the importance of pre-treatment NLR and monocyte-to-lymphocyte ratio (MLR) in lung stereotactic body radiotherapy patients. In their study, NLR and MLR were independently associated with overall survival and disease-unrelated death (358).

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 receptor (EGFR)-mutated advanced non-small-cell lung cancer patients treated with first-line EGFR tyrosine kinase inhibitors (gefitinib or erlotinib) (359).

Kos and colleagues subscribe to the importance of NLR in predicting outcome in patients with NSCLC. High NLR (≥ 3.24) proved an independent marker of poor outcome, but so did a low prognostic nutritional index (PNI). PNI < 49.5 was significantly associated with worse overall survival. PNI is calculated from the serum albumin, triceps skin-fold thickness, serum transferrin, and delayed hypersensitivity reaction (360).

According to Zhang and co-workers, preoperative NLR represents a significant prognostic indicator in primary operable NSCLC patients. NLR was reported to be an independent prognostic factor for disease-free survival and overall survival. The authors also report that, based on the NLR, high-risk patients did not benefit from adjuvant chemotherapy (361).

The prognostic significance of pretreatment NLR on survival in patients with lung cancer is confirmed by Takahashi, Xie and Berardi (362-365).

By contrast, Sim et al. report that pretreatment NLR is a prognostic factor in patients with with non-small cell lung cancer (NSCLC) receiving chemotherapy, but not in epidermal growth factor receptor (EGFR)-mutant NSCLC patients treated with tyrosine kinase inhibitors (366).

Gu and colleagues have performed a meta-analysis on the prognostic significance of NLR in patients with non-small cell lung cancer. Their results indicate that high pretreatment NLR (≥ 5.0) predicts poorer overall survival and progression-free survival (367).
Yin and co-workers confirm the prognostic significance of NLR in both non-small cell lung cancer and small cell lung cancer. In their meta-analysis, high NLR was associated with worse overall survival in both groups of cancer patients (368).

Shao and Cai report that pretreatment NLR predicts recurrence and poor prognosis for combined small cell lung cancer. In their study, a high NLR (≥ 4.15) was significantly associated with poor prognosis and recurrence of combined small cell lung cancer (369).

Shaverdian cum suis claim that, in the setting of stereotactic body radiation therapy, an elevated pretreatment NLR is a predictor of poor overall survival in patients with early-

stage non-small-cell lung cancer (NSCLC). Apart from NLR, an elevated PLR, and neutrophil count together with the presence of lymphocytopenia independently predicted for poor overall survival (370).

Tong and colleagues conclude that the systemic immune-inflammation index (SII) acts as an independent indicator of poor outomes for patients with stage III NSCL. Furthermore, the authors state that SII is superior to other inflammation-based factors in terms of prognostic ability. The SII is defined as neutrophil count × platelet/lymphocyte count (371).

Gao's group reports that preoperative pulmonary function correlates with systemic inflammatory response and prognosis in patients with NSCLC. In their single-institution retrospective analysis, preoperative forced vital capacity (FVC) and NLR were independently associated with overall survival (372).

Koh and co-workers have investigated the predictive value of NLR by examining their association with the baseline presence and subsequent development of brain metastases in patients with stage IV non-small-cell lung cancer. Patients with high NLR (≥ 4.95) had signicicantly more brain metastases at diagnosis than those with low NLR (< 4.95). Also, in patients who had no baseline brain metastasis, competing risk analysis revealed that patients with high NLR showed higher cumulative incidence of subsequent brain metastases, compared with those with low NLR. Furthermore, an increase in NLR during treatment was significantly associated with subsequent brain metastases. Therefore, the authors conclude that NLR is an independent predictive factor for the presence of brain metastases and subsequent brain metastases in stage IV NSCLC (373).

Based on the results of their meta-analysis involving over 7200 patients, Yu's group states that a high pre-treatment NLR (≥ 4.0) is significantly associated with poor overall survival, especially in cases of small-cell lung cancer. Therefore, the authors conclude that a high pre-treatment NLR may be considered as a biomarker for poor prognosis in patients with lung cancer (374).

Choi et al. have performed a retrospective study in which the effects of postoperative NSAID administration and NLR were investigated on tumour recurrence and survival in patients undergoing surgery for NSCLC. Their results show that Ketorolac administration was marginally associated wth better overall survival (p=0.05), but not with recurrence-free survival. Furthermore, preoperative NLR (≥ 5.0) was associated with a reduced recurrence-free and overall survival only in patients with stage I NSCLC. Ketorolac administration was not found to be an independent predictor of survival (375).

Dirican and colleagues report an association between intratumoural tumour infiltrating lymphocytes and NLR, and confirm their independent prognostic ability in non-small-cell lung cancer (376).

Cata and co-workers have conducted a propensity score-matched retrospective study in which the use of intraoperative dexamethasone on survival following NSCLC surgery was investigated. Their study demonstrates that intraoperative dexamethasone administration to patients undergoing NSCLC surgery is not associated with a significant impact on recurrence-free survival and/or overall survival (377).

The same group has retrospectively investigated the impact of perioperative blood transfusions on the survival of patients with NSCLC. Their results show that NLR < 5.0 and the absence of blood transfusions were significantly associated with lower mortality risk (378).

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 (379).

Yuan’s group reports that preoperative NLR is superior to PLR for survival in patients undergoing complete resection of thymic carcinoma. In their retrospective analysis, a

preoperative NLR greater than 4.1 was significantly associated with larger tumour size, reduced disease-free survival, and reduced overall survival (380).

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 to inhalational anaesthesia with sevoflurane (381).

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 (382).
These findings are confirmed by Jang and co-workers. In their mice-study, chronic stress facilitated lung tumourigenesis by promoting exocytosis of insulin-like growth factor 2 in lung epithelial cells (383).

Based on a nationwide retrospective matched population-based cohort study, Lin et al. report that long-term treatment with the β-blocker carvedilol is associated with reduced lung and gastric cancer risk (384).

Yazawa's group claims that β2-adrenergic receptor expression is an independent prognostic factor for early-stage non-small cell lung adenocarcinoma. In their retrospective study, β2-adrenergic receptor expression was independently associated with poor progression-free survival in stage I NSCLC (385).

Zingone and co-workers have investigated the relationship between anti-depressants use and lung cancer survival. Results of their retrospective analysis revealed that anti-depressants use is associated with extended lung cancer-specific survival. More specifically, norepinephrine and dopamine reuptake inhibitors and tricyclic anti-depressants use was associated with improved survival. Perchance, these findings might be attributed to the effects of these anti-depressants on the β-adrenergic receptors (386).

On the other hand, Numbere et al. were unable to confirm any protective effect of β-blockade on lung cancer risk. In their case-control study, adrenergic blocker use was not associated with a reduced risk of lung, breast, bowel and/or prostate cancer (387).

Yang and Weberpals were also unable to detect any beneficial effects of β-blocker use on outcome in patients with lung cancer (388,389).

Interestingly, Lip and colleagues have performed a cohort study in which a possible association was studied between antihypertensive drug use and cancer risk. They claim that exposure to digoxin or β-blocker therapy appears to protect against respiratory cancers while calcium antagonist therapy appears to increase the risk. Thiazide diuretics are associated with increased gastrointestinal tumour risk. Calcium antagonist use at diagnosis of breast cancer improved survival (390).

A clear forward explanation for these findings can't readily be given. Perchance that the negative dromotropic effects of digoxine and β-blockers could play an important role. In contrast to digoxine and β-blockers, most calcium antagonists and thiazide diurectics lack these negative dromotropic effects. Several study results suggest a possible association between positive dromotropic activity, respectively β-adrenergic receptor stimulation and enhanced tumour growth. Obviously, further study results are wanted.

Nonetheless, Anker's group reports that resting heart rate, independently of haemoglobin level and tumour stage, predicts survival in patients with advanced non-small-cell lung cancer, pancreatic cancer, and colorectal cancer. This conclusion is based on the results of their prospective cardiovascular sudy with a mean follow-up of 27 months (391).

Lee et al. have conducted a prospective, randomized, placebo-controlled and double-blinded trial in which the effects of dexmedetomidine on oxygenation and lung mechanics were investigated in patients with moderate COPD undergoing lung cancer surgery. Their results show that intravenous administration of dexmedetomidine during one-lung ventilation (OLV) results in higher PaO2/FiO2 ratio, lower dead space ventilation, and higher dynamic

compliance (30 and 60 minutes after OLV). In this study, patients were treated with dexmedetomidine 1.0 μg/kg as a bolus over 10 minutes, followed by a maintenance dose of 0.5 μg/kg/h during OLV (392).

In their other study, patients in the dexmedetomidine group were loaded with 1.0 μg/kg for 20 minutes before the termination of surgery, whilst patients in the control group were loaded with a comparable volume of normal saline. Patients in the dexmedetomidine group (DEX) showed lower emergence agitation and higher forced expiratory volume for 1 second (FEV1) on postoperative day 1 and 2. Furthermore, the length of hospital stay was significantly shorter in the DEX group compared with the control group. Consequently, the authors conclude that intraoperative dexmedetomidine administration could improve postoperative outcomes and reduce the length of hospital stay in patients undergoing VATS (393).

With respect to dexmedetomidine, Bulow and colleagues claim that dexmedetomidine (as an anaesthetic adjuvant) decreases the inflammatory stress response to myocardial surgery under mini-cardiopulmonary bypass. In their prospective, randomized, blinded study, dexmedetomidine reduced the circulating levels of IL-1, IL-6, TNF-α, and INF-γ, thus indicating an anti-inflammatory effect (394).
El-Shmaa and El-Baradey have reported comparable stress response attenuation by dexmedetomidine to laryngoscopy and endotracheal intubation (286).

Li et al. report that thoracic epidural analgesia decreases the mean arterial pressure and mean pulmonary arterial pressure during one-lung ventilation (OLV). Furthermore, thoracic epidural analgesia appears to be associated with a significant reduction in partial arterial oxygen pressure, mixed arterial saturation of oxygenation and increased pulmonary venous admixture fraction compared to general anaesthesia (395).

Cho et al. have performed a prospective, randomized trial in which the effects of desflurane-remifentanil anaesthesia versus propofol-remifentanil anaesthesia on arterial oxygenation during one-lung ventilation for thoracoscopic surgery were investigated. Results show that desflurane-remifentanil anaesthesia results in decreased arterial oxygenation compared with

that of propofol-remifentanil anaesthesia during one-lung ventilation in patients undergoing lung cancer surgery (396).

Liu's group claims that general anaesthesia with etomidate has less of an effect on immune function in patients with lung adenocarcinoma compared to propofol total intravenous anaesthesia. In this prospective, randomized trial the percentage of CD4+ cells in both groups (etomidate and propofol group) was significantly reduced at 24 hours post-surgery compared with the percentage before surgery, whereas the percentage of CD8+ was higher at 24 hours post-surgery. Mature T-helper cells express the surface protein CD4 and are referred to as CD4+ T cells, whereas CD8+ cells represent specific cytotoxic T-cells. The CD4+ percentage of group E (Etomidate) was higher than that of group P (Propofol) postoperatively, wheras the CD8+ percentage was lower than that of group P before surgery. One could speculate that transient suppression of the adrenal cortex might play a role (397).

Interestingly, Zhao and colleagues report that comprehensive psychological intervention can effectively relieve pain, improve immune function and enhance quality of life in patients undergoing surgery for lung cancer. In this study, the effects on postoperative pain and the immune function were analyzed until 48 hours after surgery (398).

2.2 Mesothelioma

Study results focussing on mesothelioma and its relation to anaesthesia and/or anaesthesia techniques are scarce. We could identify only the following 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 (399).

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) (400).

Based on the results of their meta-analysis, Chens and colleagues report that elevated NLR could be a potential prognostic factor for malignant pleural mesothesioma patients and might be associated with histology as an efficient clinical index to stratify patients (401).

Yamagishi et al. have evaluated the clinical value of lymphocyte-to-monocyte ratio (LMR) in relation to overall survival in patients with malignant pleural mesothelioma. Furthermore, the authors have compared the prognostic value of LMR with other inflammation-based scores in predicting survival. They claim that LMR is an independent prognostic marker for overall survival in patients with malignant pleural mesothelioma and that LMR is superior to other inflammation-based scores with respect to prognostic ability (402).

3. Breast cancer

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, evidence exists that surgery and surgical stress can lead to accelerated development of (micro) metastases (403). 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 (404).
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 (405).
However, Li's group shows that dexamethasone induces docetaxel and cisplatin resistance partially through up-regulating Krüppel-like factor 5 in triple-negative breast cancer (406).

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 (407).

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 (408).

Simonsson et al. state that COX-2 expression in breast cancer depends on oral contraceptive history, preoperative NSAID use, and tumour size. In other words, COX-2 expression in these cancer patients depends on both host factors and tumour characteristics (409).

Serra et al. failed to demonstrate a positive association between COX-2 expression and clinocopathological breast cancer subtype, tumour features and prognosis (410).
In turn, Cheuk and co-workers report that prostaglandin E2 receptors regulate metastasis through downregulation of SLC19A3 (411).

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% (412).

Based on the results of their prospective cohort study, Kim and co-workers report that NSAID use, particularly aspirin, may reduce the risk of breast cancer among premenopausal women. Furthermore, women with a sister with breast cancer are themselves at increased risk and might benefit the most from this chemoprevention (413).

Based on the results of the Iowa Women's Health Study, Vaughan and colleagues state that aspirin use may prevent breast, colon, pancreatic, and ovarian cancer in elderly women (414).

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 (415).

Interestingly, Thill and co-workers point out that the combination of vitamin D (calcitriol) and celecoxib demontstrates a cooperative growth-inhibiting effect in breast cancer cell lines (416).

Cho et al. have compared two methods of perioperative anaesthesia and analgesia on immune function in patients undergoing breast cancer surgery. In this prospective, randomized study, propofol-remifentanil anaesthesia with postoperative ketorolac analgesia (propofol-ketorolac group) was compared with sevoflurane-remifentanil anaesthesia with postoperative fentanyl analgesia (sevoflurane-fentanyl group). Results show that propofol anaesthesia with postoperative ketorolac analgesia results in an increase in NK cell cytotoxicity (NKCC), whilst sevoflurane-remifentanil anaesthesia with postoperative fentanyl analgesia results in a decrease in NKCC. Therefore, the authors conclude that propofol-remifentanil anaesthesia with postoperative ketorolac analgesia has a favourable impact on immune function by preserving NKCC compared with sevoflurane anaesthesia with fentanyl analgesia in patients undergoing breast cancer surgery (417).

With respect to the use of fentanyl, Yang's group cautions its use in the clinical application in the treatment of breast cancer. In their study, fentanyl promoted breast cancer cell stemness and Epithelial-Mesenchymal Transition (EMT) by upregulating α1,6-fucosylation via the Wnt/β-catenin signalling pathway (418).

Interestingly, Goyal and colleagues have compared the effects of intravenous fentanyl with dexmedetomidine in breast cancer surgery. In this prospective trial, patients were randomly assigned to either intravenous fentanyl (loading dose of 2 µg/kg and maintenance dose of 0,5 µg/kg/h) or intravenous dexmedetomidine (loading dose of 1 µg/kg with a maintenance of 0,25 µg/kg/h) till the end of surgery. Patients treated with dexmedetomidine proved hemodynamically more stable, required less anaesthetics and showed a better recovery profile. Therefore, the authors conclude that dexmedetomidine can be used as an alternative to fentanyl in breast cancer surgery (419).

Hugo and colleagues review COX-2 expression as a predictor of survival in various cancer types, including breast cancer (420).

Li et al. expand further on the role of COX-2 and state that COX-2 functions as a key cancer-promoting factor by triggering a positive-feedback loop between macrophages and cancer cells. As we know, COX-2 acts as a rate-limiting enzyme in the metabolic

conversion of arachidonic acid into prostaglandins, especially PGE_2. Over-expression of COX-2 has been identified in various malignancies, including breast cancer, and has been shown to contribute to carcinogenesis by stimulating cancer cell proliferation, inhibiting apoptosis, increasing invasiveness and modulating inflammation and immunity. Consequently, treatment with non-selective COX-2 inhibition by NSAIDs has been shown to reduce risk for breast, lung, prostate and colon cancers (421-423).
Apart from an over-expression of COX-2 in tumour cells, the tumour microenvironment is altered and macrophages are attracted. These tumour-associated macrophages are believed to play an important role in tumour progression, metastasis and resistance to treatment by releasing chemokines, inflammatory and growth factors. Furthermore, increased infiltration of these macrophages to breast cancer is strongly associated with poor prognosis (424). Accumulating evidence suggests that COX-2 inhibitors are potential anti-cancer therapeutic agents (425).

Maity et al. report that, based on the results of their studies (using in vitro and in vivo xenograft models), acetylsalicylic acid displays strong beneficial effects in the prevention of breast carcinogenesis. Tumour cell growth is prevented by the induction of apoptosis, but self-renewal capacity and growth of breast tumour-initiating cells/breast cancer stem cells is also significantly reduced and the formation of a palpable tumour is delayed (426).

Sutton and co-workers, however, were unable to confirm that postoperative NSAID use does improve breast cancer outcomes. Their meta-analysis revealed limited evidence that the use of aspirin and non-aspirin NSAIDs may be associated with decreased breast cancer mortality and all-cause mortality in patients diagnosed with breast cancer (427).

By contrast, Dierssen-Sotos et al. report that in their case-control study most NSAIDs, but not aspirin, showed an inverse association aginst breast cancer. However, this effect appeared to be restricted to hormone positive or HER2+ cancers (428).
Van Helmond and co-workers have conducted a prospective, randomized, controlled trial in which the effects of perioperative COX-2 inhibition on hyperalgesia and persistent pain following breast cancer surgery were investigated. Apart from less pain on movement on postoperative day 5, COX-2 inhibition had no significant effect on hyperalgesia and

persistent pain following breast cancer sugery. Therefore, the authors conclude that COX-2 inhibition has limited value in preventing sensitization and persistent pain after breast cancer surgery. Central sensitization may thus play a role in the genesis of persistent postsurgical pain (429).

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 (137).

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 (156). 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.

Lee et al. also have retrospectively investigated the prognostic significance of perioperative NLR in breast cancer patients. In over 3100 patients, NLR levels were assessed in the immediate preoperative period and the postoperative periods, 1 week, respectively 1 month after surgery. Results revealed that a high NLR (> 5.2) in postoperative week 1 was significantly associated with higher breast cancer specific mortality. Therefore, the authors conclude that immediate postoperative NLR is an important prognostic marker in breast cancer patients (430).

Krenn-Pilko and co-workers endorse the significance of preoperative NLR as a prognostic factor in breast cancer patients. However, in their study a high NLR (≥ 3.0) was associated with worse disease-free survival, but not with worse overall survival (431).

Based on the results of their randomized study, Li et al. claim that the NSAID parecoxib is is able to restrain the inflammatory response and improve immune function of breast cancer patients by suppressing the elevation of NLR following modified radical mastectomy (432).

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 (433).

Based on the results of their retrospective propensity score-matched analysis, Orditura's group demonstrates that high NLR is significantly correlated with worse prognosis in Caucasian patients with early breast cancer (434).

Ulas et al. report that high pretreatment NLR (> 2.38), in HER2-positive early breast cancer patients receiving trastuzumab, is associated with shorter disease-free survival. As for PLR, no effect on disease-free survival or overall survival was observed (435).

Liu and colleagues demonstrate that both increased NLR and PLR are associated with poor survival in hormone-receptor-negative (HR-) breast cancer patients. Furthermore, NLR was independently associated with overall survival and disease-free survival, but PLR was not (436).

Chen's group also reports that pretreatment NLR (< 2.06) is associated with pathological complete response rate in breast cancer patients treated with neoadjuvant chemotherapy. Furthermore, NLR (≥ 2.1) proved to be an independent predictor of recurrence-free survival and breast cancer-specific survival in this group of patients (437).

Based on the results of their retrospective study, Xu and co-workers also conclude that pretreatment NLR and PLR may be important predictive indicators for neoadjuvant chemotherapy response in breats cancer patients (438).

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/leucocyte-lymphocyte ratio) proved prognostic for disease-free and overall survival (439).

Pistelli et al. have retrospectively investigated the association between pre-treatment NLR, disease-free survival and overall survival in patients with early triple negative breast cancer. Their results show that higher pre-treatment NLR (> 3.0) independently correlated with poor disease-free survival and overall survival. Patients with lower NLR (< 3.0), on the other hand, showed a significantly better disease-free and overall survival (440).

Iwase's group confirms the prognostic value of NLR in patients with breast cancer. In their study, an increased NLR predicted survival, even in patients with recurrent breast cancer (441).

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 (442). 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 (443).

Okuturlar and co-workers have retrospectively compared blood count parameters between breast cancer patients and matched healthy women. They report that elevated NLR (> 2.56) was significantly higher in the patient group compared to the control group (444).

Rimando and colleagues report that high pretreatment NLR is associated with all-cause mortality, but not breast cancer-specific mortality, in black and white patients with non-metastatic breast cancer. Interestingly, black patients had significantly lower NLR values than white patients (445).

Recently, Chen et al. have conducted a meta-analysis to establish the overall accuracy of NLR in the diagnosis of breast cancer. In total 4293 patients were studied. Elevated NLR was associated with worse overall survival and disease-free survival (446).
Ethier's group has recently performed a systematic review and meta-analysis in which the prognostic effects of NLR in breast cancer patients were analyzed. Results showed that high NLR is associated with worse overall survival and disease-free survival in patients with breast cancer, with a greater effect on disease-specific outcome in ER and HER2-negative disease (447).

Interestingly, Yersal and co-workers were unable to detect any significant differences for NLR and PLR with respect to breast cancer subtypes. In their study, patients were classified into three subtypes: estrogen receptor (ER)- or progesterone receptor (PR)-positive tumours were classified as luminal tumours; human epidermal growth factor receptor-2 (HER2)-overexpressed and ER-negative tumours were classified as HER2-positive tumours; and ER, PR, and HER2-negative tumours were classified as triple-negative tumours (448).

Cihan and colleagues were also not able to find any association between NLR and survival in patients with non-metastatic breast cancer who received adjuvant radio- and chemotherapy (449).

As mentioned previously and later on, neutrophils are believed to play a key role in tumour growth and metastasis.

Benevides and co-workers claim that metastatic primary tumour-infiltrating T-lymphocytes are capable of producing interleukin 17 (IL-17), which promotes tumour growth and migration of neutrophils and tumour cells to secondary disease sites. Tumorigenic neutrophils promote disease progression, produce the chemokine (C-X-C motif) ligand 1

(CXCL1), matrix metallopeptidase 9 (MMP-9), vascular endothelial growth factor (VEGF) and tumour necrosis factor (TNF). IL-17 also induces IL-6 and Chemokine (C-C motif) ligand-20 (CCL20) production in metastatic tumour cells, favouring the recruitment and differentiation of T-17 helper cells. High IL-17 expression was associated with lower disease-free survival and worse prognosis in patients with invasive ductal carcinoma of the breast. In other words, IL-17 promotes breast cancer progression by changing the behaviour of tumour cells and eliciting tumorigenic neutrophils recruitment. Since IL-17 neutralization inhibited tumour growth and prevented the migration of neutrophils and tumour cells, the authors conclude that IL-17 blockade may represent an attractive approach for the control of invasive breast cancer (450).
Li's group confirms that neutrophils play a crucial role in gastric cancer progression by the production of interleukin-17. Thus linking inflammatory stimuli to cancer progression by promoting angiogenesis (451).

Recent study results published by Barron et al. demonstrate that women with breast cancer and pre-diagnostic aspirin use (COX-1/COX-2 inhibitors) were significantly less likely to present with a lymph node-positive tumour than patients who did not use aspirin. Furthermore, pre-diagnostic 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 post diagnostic aspirin use and breast cancer-specific mortality. Based on this nationwide population-based cohort study, the authors conclude that recent pre-diagnostic aspirin use (< 1 year) is protective against lymph node-positive breast cancer (452).

Allott and colleagues report that increased duration and regularity of NSAID use is associated with reduced breast cancer-specific mortality in women with oestrogen receptor-positive cancer. There was no association for oestrogen receptor-negative patients. The authors conclude that, if confirmed, these findings support the hypothesis that potential chemo preventive properties of NSAID's are mediated (partly) through suppression of oestrogen biosynthesis (453).

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 (454).

Mohammadinejad and colleagues have performed a prospecticve, double blind, placebo-controlled, randomized trial in which the effects of celecoxib and diclofenac were studied in patients with breast cancer. Based on the results, the investigators conclude that the selective COX-2 inhibitor celecoxib appears to possess superior anti-depressive effects compared with diclofenac in breast cancer patients with mild to moderate depression (455).

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 (456). 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.

Interestingly, Huang and colleagues claim that NSAIDs and aspirin use *after* diagnosis, in contrast to before diagnosis, is associated with improved breast cancer survival, including breast cancer-specific mortality, all-cause mortality, and relapse/metastasis. This claim is based on a meta-analysis (457).

In their study on mamma carcinoma, Gupta et al showed that morphine has the ability to promote tumour proliferation (17).
Niu and colleagues even claim that morphine can contribute to chemo resistance (by expanding the population of cancer stem cells), and that it promotes tumour growth in a mouse model of breast cancer (458).

By contrast, Doornebal and colleagues claim that, based on preclinical mouse models for metastatic human invasive lobular and HER2+ breast cancer, analgesic doses of morphine do not affect mammary tumour growth, angiogenesis and the composition of tumour-

infiltrating immune cells. Furthermore, morphine administered in the presence or absence of surgery-induced tissue damage and pain, neither facilitates de novo metastatic dissemination nor promotes outgrowth of minimal residual disease. In addition, they conclude that these findings indicate that opioids can be used safely for perioperative pain management in cancer patients and emphasize that current standards of “good clinical practice” should be maintained (459).
Cronin-Fenton et al. were also unable to find any clinically relevant evidence of an association between opioid prescriptions and breast cancer recurrence in their prospective cohort study (460).

Hozumi’s group reports that intraoperative remifentanil use is independently associated with an increased risk of postoperative nausea and vomiting in elective mastectomy under general anaesthesia. In this retrospective observational study this association was dose-dependent (461).

Hetta et al. demonstrate in their prospective, randomized trial that a single preoperative dose of pregabalin 150 mg is an optimal dose for reducing postoperative pain and morphine consumption in patients undergoing modified radical mastectomy for breast cancer (462).

Satomoto and colleagues report that a low dose of droperidol (20 µg/kg) decreases the desflurane concentration needed during breast cancer surgery without adverse effects. This claim is based on the results of their prospective, randomized, double-blinded study (463).

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 (464). 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 (465).

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 (466).

Several studies have demonstrated that loco-regional analgesia, such as paravertebral blockade, results in more effective pain control and also in less adverse effects (46,467-472). 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) (473).

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 (474).

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 (475).

Based on the results of their prospective observational study, Perez Herrero and colleagues report that general anaesthesia combined with paravertebral block is as effective as general anaesthesia combined with serratus-intercostal blockade in improving the quality of postoperative recovery after breast cancer surgery (476).

Tam et al. have performed a meta-analysis of randomized controlled trials on the effects of wound infiltration in breast-conserving cancer surgery. They report that local wound infiltration with ropivacaine or bupivacaine significantly decreases pain at only two hours postoperatively. At 12 and 24 hours postopeartively no pain reduction was detected. Moreover, no significant effect on postoperative analgesic consumption was monitored (477).

By contrast, Abdelsattar and co-workers report that intraoperative local infiltration of liposomal bupivacaine in patients undergoing mastectomy with immediate tissue expander reconstruction decreases narcotic requirements in the recovery room (PACU), shortens preoperative anaesthesiology time, and provides similar, if not better, perioperative pain control compared with paravertebral blockade (478).

With respect to liposomal bupivacaine, Rice et al. have characterized the pharmacokinetic and safety profiles of liposomal bupivacaine following a repeated subcutaneous dose in healthy volunteers. Their results showed that the mean ± standard deviation maximum observed plasma concentration (C_{max}) following a repeated dose of liposomal bupivacaine remained well below accepted values for central nervous system and cardiac toxicity. Liposomal bupivacaine was well-tolerated and revealed no clinically important safety signals (479).

Wolf and co-workers have prospectively investigated the effects of additional paravertebral blockade (PVB) on pain and opioid requirement in patients undergoing prosthetic breast reconstruction surgery. The addition of PVB to general anaesthesia resulted in a significantly lower opioid requirement both intra- and postoperatively. Furthermore, significantly lower pain scores were reported by patients in the PVB-group (up to 6 hours postoperatively), and less anti-emetics were consumed (480).

Fahy et al. confirm that PVB results in decreased opioid use and decreased need for postoperative anti-emetic medication in patients undergoing mastectomy. The greatest benefit of PVB was seen in patients undergoing bilateral mastectomy with immediate beast reconstruction (481).
Parikh’s group even reports that preoperative PVB, apart from improving postoperative pain control, also shortens hospital stay for patients with breast cancer undergoing postmastectomy autologous reconstruction (482).

Based on the results of their randomized and double-blinded trial, Župčic and co-workers state that the use of 0.5% levobupivacaine solution for PVB (in comparison with 0.5%

levobupivacaine with 2% lidocaine) results in a longer time-to-block onset, but also reduces hemodynamic disturbances and prolongs analgesic effect (483).

In turn, Mayur et al. conclude that clonidine as an adjuvant in PVB provides more profound analgesia for up to 48 hours postoperatively in patients undergoing breast cancer surgery without any appreciable side effects (484).

Based on the results of their prospective and randomized study, Jin and colleagues arrive to the same conclusion regarding the addition of dexmedetomidine to bupivacaine in PVB. The addition of dexmedetomidine resulted in prolonged duration and more profound analgesia without serious adverse events (485).

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) (486).
However, Cata's retrospective study results do not support the hypothesis that the use of PVB is associated with longer survival after surgery for breast cancer (487).

Finn's group has also performed a pilot study in which the effects of a single shot and continuous paravertebral blockade on post-mastectomy cancer recurrence were investigated. In this prospective, randomized, triple-masked, placebo-controlled investigation, 54 patients undergoing either unilateral or bilateral mastectomy were included and received unilateral or bilateral PVB corresponding to the surgical site. Subsequently, patients received either ropivacaine 0.4% or normal saline via the perineural catheter until catheter removal on postoperative day 3. Cancer recurrence from the day of surgery until 2 years post surgery was investigated via chart reviews. Results of this small pilot study showed no evidence that extending a single-injection paravertebral block with a multi-day perineural local anaesthetic infusion decreases the risk of post-mastectomy cancer recurrence (488).

Karmakar et al. have conducted a 5-year follow-up analysis of a randomized controlled trial in which the effects of TPVB on survival in patients undergoing radical mastectomy were investigated. Based on their results, the authors conclude that, although the original study

was underpowered to properly address long-term outcomes, it appears that TPVB, administered whether as a single-shot or continuous infusion during the perioperative period, has little to no appreciable effect on local recurrence, metastasis or mortality after breast cancer surgery (489).

Based on the results of their systematic review, Perez-Gonzalez and colleagues conclude that there are no data to support or refute the use of paravertebral blocks for reduction of cancer recurrence or improvement in cancer-related survival. However, PVB use is associated with lower levels of inflammation and a better immune response in comparison with general anaesthesia and opioid-based analgesia (490).

Syal and Chandel have performed a randomized, double blind trial in which the postoperative analgesic effects of PVB, pectoral nerve block, and local infiltration in patients undergoing modified radical mastectomy were compared. Patients were randomly assigned to the local infiltration, PVB, or pectoral nerve block group. All patients received 21 ml 0.5% bupivacaine with epinephrine *at the end of surgery* prior to extubation. Patients in the local infiltration group received infiltration at the incision site. Patients in the PVB group received ultrasound-guided ipsilateral paravertebral blockade, and patients in the pectoral nerve block group received ultrasound-guided PECS blocks I and II.
Based on their results, the authors conclude that ultrasound-guided PVB reduces postoperative pain scores, prolongs the duration of analgesia, and decreases demands for rescue analgesics in the first 24 hours postoperatively compared to ultrasound-guided PECS blocks and local infiltration. Obviously, any pre-emptive mode of action has been abolished by the administration of the blockades at the end of surgery (491).

Compagnone and co-workers underline the value of paravertebral blockades in older patients undergoing elective mastectomy in one-day surgery (492).

Cali Cassi’s group expands further on the benefits of PVB in breast cancer surgery. Apart from superior pain control, reduction of opioid consumption, decrease in postoperative nausea and vomiting, and overall decrease in length of hospital stay, the authors also state that some studies suggest that the use of regional anaesthesia-analgesia might attenuate

perioperative immunosuppression and minimize metastases in breast cancer patients. Therefore, they conclude that PVB seems to provide the most benefits in patients undergoing an unilateral or bilateral mastectomy followed by immediate reconstruction (493).

However, Albi-Feldzer et al. present a case report in which ultrasound-guided thoracic paravertebral blockade is complicated by total spinal anaesthesia (494).

Tsigonis and colleagues claim that locoregional anaesthesia has no effect on breast cancer outcomes compared to general anaesthesia. In their retrospective study, breast cancer patients were retrospectively divided into 2 groups: those who received only locoregional anaesthesia (LRA) and those who received general anaesthesia (GA). No significant differences in overall survival, disease-free survival and local regional recurrence were found between the two groups (495).

Kairaluoma et al. report similar findings. In their retrospective study involving breast cancer surgery, 45 patients had received a PVB and 41 patients had received a SHAM block. The reported median follow-up time of these patients was 12 years. There were no statistically relevant differences between both groups with respect to disease-free survival, distant recurrence-free survival, breast cancer-specific and overall survival (496).

Agarwal et al. report that single-injection thoracic paravertebral blockade significantly decreases pain scores in patients undergoing mastectomy. However, this reduction in pain scores appears to be limited to the immediate postoperative period (497).
With respect to mastectomy with direct reconstruction, Glissmeyer and colleagues demonstrate that thoracic paravertebral analgesia reduces the use of opioids (498).

Pei and colleagues have performed a randomized, controlled trial in which the effects of ultrasound-assisted thoracic paravertebral blockade (TPVB) on opioid consumption and postoperative pain were investigated in patients undergoing breast cancer surgery. Their results clearly indicate that the combination of paravertebral blockade and propofol

anaesthesia reduces intraoperative volatile anaesthetic and opioid requirements, and results in less postoperative pain in patients undergoing breast cancer surgery (499).

Based on the results of their randomized, double-blinded study, Sahu and colleagues conclude that single-injection thoracic paravertebral blockade with ropivacaine (0.375% in a dose 0.25 ml/kg) has the same analgesic potency as a single-injection PVB with bupivacaine (0.375% in a dose 0.25 ml/kg) in patients undergoing modified radical mastectomy. However, bupivacaine got better postoperative VAS scores in mean and after the 1th, 6th, and 24th postoperative hour (500).

Amaya et al. have performed a meta-analysis in which the effects of analgesics (used for acute pain treatment) on the major co-morbidities following breast cancer surgery were investigated. Their results show that in general the use of regional analgesics (paravertebral blockade) has a beneficial effect on the occurrence of comorbidity (501).

Pace and co-workers report that the routine use of a single-injection, transverse, in-plane ultrasound-guided technique for TPVB in patients undergoing mastectomy with immediate breast reconstruction is associated with very few complications. Six complications were identified in a total of 1427 thoracic paravertebral injections. Half of these complications involved bradycardia and hypotension: a vasovagal episode in 1 patient, and evidence of possible local anaesthetic toxicity in 2 patients. There was no incidence of suspected accidental pleural puncture or symptomatic pneumothorax identified (502).

Two studies revealed that the use of local anaesthetics, in either paravertebral of epidural blockade, might result in a lower probability of developing chronic pain (503,504).

With respect to chronic pain following (minor) surgery for breast cancer, Fuzier and colleagues report that 40% of patients experiences pain up to 3 months following surgery. Furthermore, in 61% of the cases pain has a neuropathic component. Most surgeries in this prospective cohort study involved general anaesthesia with no regional analgesia technique, laryngeal mask, sufentanil and propofol for induction, and multimodal analgesia during the postoperative period (505).

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 (506).

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 (507).

Steyaert and colleagues have conducted a cross-sectional survey in which the effects of the perioperative analgesic/anaesthetic regimen on long-term chronic pain following mastectomy were investigated. Their study results confirmed the high prevalence of chronic postmastectomy pain (CPMP)(44%). Recall of preoperative pain, chemotherapy, and need for strong opioids in the postanaesthesia care unit (PACU) were all associated with the presence of chronic pain. Remarkably, of the intraoperative analgesics/anaesthetics studied, only the use of halogenated agents was associated with a lower prevalence of CPMP (508).

Lee et al. even claim that there is a possibility that propofol-based total intravenous anaesthesia (TIVA) for breast cancer surgery can reduce the risk of recurrence during the initial 5 years after modified radical mastectomy. This claim is based on the results of their retrospective study in which propofol-based TIVA was compared with sevoflurane-based anaesthesia in patients undergoing modified radical mastectomy for breast cancer. The propofol group showed a significantly lower rate of cancer recurrence compared with the sevoflurane group. Also, the use of opioids during the perioperative period was greater in the propofol group than in the sevoflurane group (509).

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 (510).

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 (511).

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 (512).

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 (46).

Buckley and colleagues have investigated the effect of serum from women undergoing primary breast cancer surgery on healthy human donor natural killer (NK) 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 (513).

Desmond and co-workers claim that anaesthetic technique does have an effect on immune cell infiltration in breast cancer. This claim is based on the results of their study, in which propofol-paravertebral anaesthesia with continuing analgesia induced increased levels of NK-cell and T-helper cell infiltration into breast cancer tissue compared with balanced

general anaesthesia with opioid analgesia. The authors conclude that anaesthetic technique may affect perioperative immune function conducive to breast cancer recurrence and metastasis (514).

Woo and colleagues have prospectively investigated the effect of propofol and desflurane on the immune response in breast cancer patients. Patients undergoing breast cancer surgery were randomly assigned to receive either propofol (n=20) or desflurane (n=20) anaesthesia. Total and differential white blood cell counts together with lymphocyte subpopulations were determined before, and 1 hour after induction of anaesthesia and at 24 hours after surgery. Results showed that both propofol and desflurane anaesthesia preserve the IL-2/IL-4 and CD4(+)/CD8(+) T-cell ratio. Total leucocytes were lower in the propofol group than in the desflurane group at 1 hour after induction and 24 hours postoperatively. Furthermore, the number of NK-cells decreased significantly 1 hour after induction in the propofol group, but not in the in the desflurane group. Therefore, the authors conclude that both propofol and desflurane anaesthesia for breast cancer surgery induce a favourable immune response in terms of preservation of IL-2/IL-4 and CD4(+)/CD8(+) T-cell ratio in the perioperative period. With respect to leucocytes and NK cells, desflurane anaesthesia appears to be associated with less adverse immune responses than propofol anaesthesia during breast cancer surgery (515).

Kim’s group has investigated the differences in immune response to anaesthetics used for day surgery versus hospitalization surgery in breast cancer patients. Patients in the day surgery group received lidocaine, propofol and pethidine, whilst patients in the hospitalization group were treated with propofol, systemic opioids and sevoflurane. Results revealed few differences in immune response beween the two groups (516).

Ramirez et al. have studied the innate immune function after breast, lung, and colorectal cancer surgery. They demonstrate that postoperative function of NK cells is significantly reduced compared with preoperative levels. However, NK cell function was similar among the different types of surgery, whereas the postoperative plasma concentration of epinephrine was significantly increased. The authors conclude that the magnitude of innate immune suppression is similar among different oncological procedures (517).

However, it remains unclear whether the function of NK cells was primarily influenced by surgery itself or by the anaesthetics used.

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 (518).

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 (519).
Mohta and co-workers confirm these findings. In their prospective, randomized, double blind study thoracic paravertebral blockade (TPVB), using dexmedetomidine (1 μg/kg) added to bupivacaine 0.5% (0.3 ml/kg) in patients undergoing major breast cancer surgery under general anaesthesia, provided analgesia of longer duration with decreased postoperative opioid consumption and lower incidence of nausea and/or vomiting compared to TPVB with bupivacaine alone or no TPVB (520).

With respect to dexmedetomidine, Fan et al. report that during the first 24 hours following mastectomy, patients receiving dexmedetomidine have lower NRS pain scores, decreased morphine consumption, longer time to first morphine request as well as a trending decreased incidence of adverse effects when compared to those who do not receive dexmedetomidine (521).

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 (522).

Coopey et al. claim that the use of preoperative paravertebral blockade decreases length of stay in patients undergoing mastectomy followed by immediate reconstruction (523).

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 (524).

Based on the results of their randomized study, Fallatah and Mousa report that multiple levels paravertebral blockade is an effective regional technique for postoperative pain management. It provides superior analgesia with less narcotics consumption, and fewer side-effects compared with patient-controlled analgesia with morphine for patients with breast cancer who undergo unilateral lumpectomy with axillary lymph node dissection (525).

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 (526).

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 (527).

Ilfeld et al. report that adding a multiple-day continuous ropivacaine infusion to a single-injection ropivacaine paravertebral nerve block may result in a lower incidence of pain as

well as pain-related physical and emotional dysfunction 1 year after mastectomy. This is based on the results of a prospective 1-year follow-up assessment of a randomized, triple-masked, placebo-controlled study in which the effects of an additional continuous ropivacaine infusion to a single-injection PVB were investigated (528).

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 (529).
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 (530).

In their review, Chen and colleagues discuss the effect of paravertebral blockade in combination with propofol anaesthesia on breast cancer metastasis and progression (531).

Zhong et al. have conducted a randomized, double blind, placebo-controlled trial in which the effects of transversus abdominis plane (TAP) blockade on opioid consumption following microsurgical abdominal tissue breast reconstruction were investigated. Results show that pre-closure TAP blockade with bupivacaine results in a significant reduction of opioid consumption on the first postoperative day only compared with TAP blockade with saline. However, there were no significant differences in nausea, anti-nausea medication, sedation scores, Quality of Recovery Score, time to ambulation, and hospital stay duration (532).
These findings are in accordance with previous studies showing that pre-emptive analgesia has more impact on pain and the inflammatory stress response than pre-closure and postoperative interventions (79,302).

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 (57). Lirk and colleagues, in turn, report that lidocaine and ropivacaine, but not bupivacaine, demethylate deoxyribonucleic acid in breast cancer cells in vitro, thus reactivating tumour suppressor genes and inhibiting tumour growth (58). Chang et al. demonstrate that both lidocaine and bupivacaine induce apoptosis in human breast cancer cells (60).
Votta-Velis and co-workers state that amide-linked local anaesthetics attenuate tumour cell migration and signalling pathways enhancing tumour growth and metastasis (70).

Based on their meta-analysis, Faria et al. conclude that thoracic paravertebral blockade reduces postoperative analgesic requirements, compared to placebo, in patients undergoing breast cancer surgery (533).

Koonce and colleagues have performed a retrospective, case control study of patients undergoing breast cancer surgery receiving regional, regional and general, or general anaesthesia. Univariate analysis showed the use of regional anaesthesia to trend towards reduced cancer recurrence, but it did not achieve statistical significance (p=0.06) (534).

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 (535).
These findings are in shrill contrast to earlier study results that ascribed unfavourable properties to propofol in relation to the progression of cancer (21).

Recently new techniques have been described for pain management in major breast surgery: the serratus-intercostal block, the serratus plane block, the pectoralis-serratus interfascial block, the paravertebral lamina technique and the pectoral nerves I, and II blocks (472,536-543). Until now, no study results have been published regarding the effectiveness of these techniques in relation to breast cancer outcome and/or recurrence.

Hards et al. claim that the serratus plane block provides effective regional analgesia, suitable for mastectomies, and currently appears to be superior to wound infiltration alone (536).

Hetta and Rezk report that the pectoralis-serratus interfascial plane block is safe and easy to perform and decreases the intensity of postmastectomy pain. However, this technique proved inferior to thoracic paravertebral blockade with respect to its analgesic effects (538).

Abdallah's group confirms that both pectoralis and serratus blocks are associated with a reduction in postoperative in-hospital opioid consumption and PONV compared with conventional opioid-based analgesia following ambulatory breast cancer surgery (539).

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 (540).
Kulhari's group even claims that the Pecs II block provides superior postoperative analgesia than the thoracic paravertebral block in patients undergoing modified radical mastectomy, without causing any adverse effects (541).

M and co-workers have prospectively investigated the effects of pectoral nerve blocks on analgesia following breast cancer surgery. In their randomized study, ultrasound-guided PECS I and II blocks resulted in lower opioid consumption, longer time to first analgesic requirement, and less limitation of shoulder movement on the operative site at 4 hours and 5 hours after surgery compared to general anaesthesia alone. However, there was no effect on postoperative nausea and vomiting (542).

Rice and colleagues report that the posterior intercostal nerve block with liposomal bupivacaine may be considered as a suitable alternative to thoracic epidural analgesia in major thoracic surgery. The use of liposomal bupivacaine is reported to offer the potential to provide prolonged blockade of intercostal nerves for up to 72 to 96 hours. However, in order to cover the surgical site adequately the blockade has to be delivered at multiple levels (543,544).

Based on the results of their randomized, double blind and placebo-controlled study, Versyck et al. report that the PECs II block reduces postsurgical opioid consumption during the Post Anaesthesia Care Unit (PACU) stay time for patients undergoing breast cancer surgery (545).

Kamiya's group concludes that PECS block combined with general anaesthesia reduces the requirement for propofol but not that for remifentanil. Furthermore, the PECS block

improved postoperative pain but not the postoperative quality of recovery following breast cancer surgery (546).

Chakraborty et al. describe a single-injection technique (COMBIPECS) combining both Pecs I and Pecs II blocks in a single needle pass. They claim that this technique saves time and is equally effective as the modified Pecs block, which uses 2-needle passes (547).

Based on the results of their prospective, randomized, double blind study, Othman's group claims that the addition of ketamine (1 mg/kg) to the modified Pecs block (30 ml of 0.25% bupivacaine) prolongs the time to first request for analgesia and reduces total opioid consumption without serious side effects in patients undergoing modified radical mastectomy (548).

Takahashi and Suzuki describe the complete antethoracic block, comprising of the antethoracic medial, antethoracic inferior, and antethoracic lateral blocks, as a suitable block for modified radical mastectomy (549).

Li, Yu and Hung report that, compared with the placement of a paravertebral block alone, the combination of blocks targeting the pectoral musculature with a PVB for modified radical mastectomy reduces the sedative and analgesic requirements during surgery and provides more effective postoperative analgesia (550).

Until now, no study results have been published regarding the effectiveness of the posterior intercostal nerve blockade with liposomal bupivacaine in relation to breast cancer growth and/ or recurrence.

Veiga and colleagues describe the erector spinae plane (ESP) block and suggest that this plane block might be a promising new technique in the context of surgical pain treatment during radical mastectomy (551).
Bonvinci and co-workers discuss the benefits of bilateral ultrasound-guided erector spinae plane blocks in breast cancer and breast reconstructive surgery (552).

In addition, Forero's group presents a case series in which the ESP block was successfully used in the management of post-thoracotomy pain syndrome (553).
Clearly a promising new technique and we eagerly await further study results.

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 (554).

Channabasappa and colleagues report that the addition of dexmedetonidine to low dose ropivacaine for cervical epidural analgesia can shorten the onset of sensory block and extend the duration of analgesia with optimum sedation without episodes of hypoxaemia as compared to the addition of clonidine to ropivacaine in patients undergoing modified radical mastectomy. In this prospective, randomized, double blind study patients received 15 ml of 0.375% ropivacaine combined with 1 μg/kg of dexmedetomidine (555).

It has to be mentioned that cervical epidural analgesia is not routinely used in the operating theatre in our hospital.

Lou et al. have performed a retrospective analysis in which the effects of combined epidural and general anaesthesia were investigated in patients undergoing free flap breast reconstruction. They conclude that the combination of epidural analgesia and general anaesthesia improves postoperative pain and side effects without increasing the risk of flap thrombosis (556).

Claroni's group reports that sevoflurane preconditioning has a protective effect on ischaemia-reperfusion injury in patients undergoing reconstructive plastic surgery with microsurgical flap. However, this protective effect is expressed in the early postoperative hours and does not persist in the long-term (557).

With respect to breast reconstruction following breast cancer surgery and based on the results of their matched controlled study, Kronowitz and co-workers conclude that lipofilling of the breast does not increase the risk of recurrence of breast cancer (558).

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 (559).

Based on the results of their meta-analysis of randomized controlled trials, Rai and colleagues report that gabapentin and pregabalin seem to reduce opioid consumption in the PACU following breast cancer surgery. However, gabapentin, but not pregabalin, reduced pain at 24 hours after surgery. Neither drug affected the development of chronic postoperative pain (560).

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 (561).

Kim et al. have investigated the effects of systemic lidocaine versus magnesium administration on postoperative functional recovery and chronic pain in patients undergoing breast cancer surgery. The results of this prospective, randomized, double blind trial revealed that intraoperative infusion of lidocaine (2 mg/kg as a bolus followed by 2 mg/kg/h

continuous infusion) improved the quality of recovery and attenuated the intensity of chronic pain in these patients (562).

Based on the results of their randomized, double-blind, and placebo-controlled trial, Kendall et al. report that intravenous lidocaine infusion reduces the incidence of pain at rest at 6 months following breast cancer surgery. However, pain with activity, pain qualities, and the physical or emotional impact of pain remained unaffected. In this study, patients were treated with either intravenous lidocaine (1.5 mg/kg bolus followed by a 2 mg/kg/hour infusion) or normal saline at the same bolus and infusion rate. Evaluation for the presence of chronic persistent postsurgical pain took place at 3 and 6 months after surgery (563).

Christie's group has investigated the effects of additional lidocaine to a tumescent solution with dilute epinephrine in breast reduction surgery. Based on the results of this randomized trial, they conclude that the addition of lidocaine to tumescent solution does not significantly affect postoperative pain following breast reduction surgery. Although the use of tumescent solution with dilute epinephrine has been shown to significantly decrease operative blood loss, the addition of lidocaine had no effect on total intravenous narcotic use, 24-hour narcotic use, peak pain scores in the post-anaesthesia care unit and 24 hours postoperatively, and the incidence of nausea and vomiting (564).

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.

Based on the results of their meta-analysis, Cheng and Ilfeld report that procedural interventions involving locoregional blockades are more conclusively effective than pharmacologic modalities in providing analgesia to patients following breast cancer surgery (565). Furthermore, the same authors conclude that of the currently different promising analgesic techniques for breast surgery, thoracic epidural analgesia and paravertebral nerve blockades are the only analgesic techniques that provide potent, consistent perioperative pain control following breast surgery (566).

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, a correlation has been reported between stimulation of the beta-adrenergic system and increased chance of developing metastases (183-187). 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 in the papers published by Botteri and De Giorgi (184,185). 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.

Based on the results of their prospective, randomized study, Zhou and colleagues report that propranolol has the potential to alleviate surgical stress-induced elevation of regulatory T-cells (Tregs) in breast cancer patients. Epinephrine markedly promoted Treg proliferation, whereas propranolol prevented such enhancement effect (567).

Shaashua and co-workers have performed a prospective, randomized, placebo-controlled trial in which the effects of perioperative COX-2 and β-adrenergic blockade on metastatic biomarkers in breast cancer patients were evaluated. Based on their results, they conclude that perioperative inhibition of COX-2 and β-adrenergic signalling provides a safe and effective strategy for inhibiting multiple cellular and molecular pathways related to metastasis and disease recurrence in early-stage breast cancer (568).

Childers et al. have performed a meta-analysis on the effects of β-blockers on breast cancer outcomes. Results of this systematic review and meta-analysis suggest that the use of β-blockers significantly reduces risk of breast cancer death among women with breast cancer (569).
Wang and colleagues support these findings in their meta-analysis (570).

Zhao et al. also conclude that β-blockers can reduce the risk of breast cancer recurrence in female hypertensive patients. However, in their systematic review, the use of angiotensin-converting enzyme inhibitors (ACEi) and calcium channel blockers (CCB) was unrelated to breast cancer risk (571).
By contrast, Ni and co-workers report that long-term use of ACEi and angiotensin-receptor blockers (ARBs) was associated with an significantly reduced breast cancer risk in their meta-analysis of observational studies (572).

Spera's group concludes that β-blocker intake is associated with significant improvement in progression-free survival, particularly in patients with triple-negative breast cancer and patients not previously exposed to β-blockers. This conclusion is based on the results of their retrospective analysis (573).

Parada-Huerta and co-workers report that in Mexican breast cancer patients, treatment with non-selective beta-adrenergic receptor blockers is associated with a decreased risk for metastasis at the time of diagnosis (574).

However, and as mentioned previously, Numbere et al. were unable to confirm any protective effect of β-blockade on breast cancer risk. In their case-control study, adrenergic blocker use was not associated with a reduced risk of breast, lung, bowel and/or prostate cancer (387).
Kim's group has performed a meta-analysis in which the effects of β-blockade on breast cancer were analyzed. Their results fail to demonstrate any beneficial effect of β-blocker use on overall survival, cancer-specific survival, and/or recurrence of breast cancer (575).

Wilson and colleagues support the finding that β-adrenergic stimulation might facilitate the process of metastasizing. In their study, β-adrenergic receptor stimulation suppressed Rap1B prenylation, thereby reducing cell-to-cell adhesion and promoting cell scattering. Rap1B is a GTPase that suppresses the metastasis of breast cancer cells by increasing cell-to-cell adhesion. Furthermore, breast cancer cell migration was decreased by the β-blocker propranolol (576).

Pon and co-workers report that the β2-adrenoreceptor activates a positive cAMP-calcium feedforward loop to drive breast cancer cell invasion (577). Thus, underlining the importance of β-adrenergic receptor stimulation on breast cancer growth.

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 (578).

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 (579).

Kim's group demonstrates that activation of β-adrenergic signalling by β-adrenergic receptor agonists reduces deformability of highly metastatic human breast cancer cells, and that these stiffer cells are more invasive in vitro. In a similar way, β-adrenergic receptor activation also reduces the deformability of ovarian, prostate, melanoma and leukaemia cells. These changes in cell deformability can be prevented by pharmacological β-blockade (580).

Montoya and co-workers conducted a retrospective cross-sectional study in 404 breast cancer patients in which the effects of β-adrenergic receptor antagonists on breast cancer growth were investigated. Results showed that non-selective β-blockers, but not selective β-blockers, reduced tumour proliferation by 66% in early stage breast cancer compared to non-users (581).

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 (582).

Sakellakis et al. were also unable to demonstrate any potential anti-tumour effects of β-blockers in patients with breast cancer. In this retrospective study, disease-free survival did not differ between β-blockers users and non-users (583).

On the other hand, Melhem-Bertrandt et al. did find an association between beta-blocker use and survival in patients with breast cancer. In their retrospective study, which consisted of 1413 breast cancer patients who received neoadjuvant chemotherapy, beta-blocker use at the start of chemotherapy was associated with a significantly better relapse-free survival, but not overall survival. This was also the case in patients with triple-negative breast cancer (584).

Choy et al. also investigated the effects of perioperative beta-blocker use on proliferation and migration of breast cancer cells and breast cancer recurrence. The results of their restrospective study revealed that perioperative β-blockade in stage II breast cancer patients was significantly associated with decreased cancer recurrence. Furthermore, triple-negative brain-metastatic cells also exhibited increased cell proliferation and migration in response to β2-adrenergic receptor activation. These effects were abrogated by the beta-blocker propranolol. Propranolol decreased β2-adrenergic receptor-activated invasion. In vivo, propranolol treatment of triple-negative metastatic cells decreased the establishment of brain metastases. Therefore, the authors conclude that stress and the corresponding β2-receptor activation may promote the stablishment of brain metastases of triple-negative breast cancer cells. In addition,these results suggest a benefit to perioperative beta-blockade during surgery-induced stress with respect to breast cancer recurrence and metastases (585).

Powe and colleagues report similar findings. In their proof-of-principle study, beta-blocker treatment significantly reduced distant metastases, cancer recurrence, and cancer-specific mortality in breast cancer patients (586).

In turn, Zhong and co-workers conclude that beta-blocker use *after* diagnosis, but not *before*, is beneficial for the survival of cancer patients. This conclusion is based on the results of a meta-analysis, in which beta-blocker use after diagnosis was significantly associated with all-cause mortality and cancer-specific mortality. Pre-diagnostic beta-

blocker use showed no beneficial effect on on all-cause mortality or cancer-specific mortality. Interestingly, only breast cancer patients who used beta-blockers after diagnosis had a prolonged overall survival (587).

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 (588).
The same group reports that catecholamines, through β-adrenergic receptor stimulation, appear to be involved in mammary gland development, inducing mature duct formation (589).

As mentioned previously, Lip and colleagues have performed a cohort study in which they studied the use of antihypertensive drugs on cancer risk. They claim that the use of calcium antagonists at the time of diagnosis of breast cancer was associated with impoved survival (390).

Goldvaser and colleagues have retrospectively investigated the effects of angiotensin receptor blocker usage on breast cancer characteristics. Strikingly, their results reveal an association between angiotensin receptor blocker use and more advanced breast cancer disease (590).

Raimondi et al. have performed a systematic review and meta-analysis in which the use of beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on breast cancer survival was studied. Their results show that patients treated with beta-blockers at the time of breast cancer diagnosis had a significantly longer breast cancer specific survival compared with non-users. There was also a borderline significant improvement in disease-free survival for patients treated with beta-blockers. No association of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blocker use with disease-free and overall survival was found (591).

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 α2-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 α2-adrenergic blockade by efaroxan also increased primary tumour size and distant metastasis under non-stress conditions, but selective α1- adrenergic blockade by prazosin did not.
Therefore, the authors conclude that these results are consistent with the hypothesis that α2-adrenergic signalling can act through an auto receptor mechanism to inhibit adrenergic catecholamine release, and thus modulate established effects of β-adrenergic signalling on tumour-relevant biology (592).

In their review, Obeid and Conzen expand further on the role of adrenergic signalling in breast cancer biology (593).

Based on the results of their nationwide cohort study involving 61873 patients, Søgaard and co-workers report that patients with hyperthyroidism show an increased risk of breast

cancer, whilst patients with hypothyroidism show a decreased risk. Therefore, the authors conclude that thyroid function level and breast cancer risk may be associated (594).
A plausible explanation for this finding may be the difference in β-adrenergic receptor stimulation. Patients with hyperthyroidism are known to experience β-adrenergic hyperactivity compared with patients suffering from hypothyroidism.
As stated by Bachman et al., there is evidence that the efficacy of clinical treatment of hyperthyroidism is due to antagonism of sympathetic signalling (595).

Interestingly, Akbari et al. report that spiritual intervention (psychotherapy) is capable of altering dopamine receptor gene expression in breast cancer patients, thus potentially affecting the growth of tumour cells (596).

Chen's group demonstrates that psychological stress can promote lung metastatic colonization of circulating breast cancer cells by creating a pre-metastatic niche through the activation of β-adrenergic signaling. Thus, β-adrenergic signalling can promote lung metastatic colonization by tumour cells through increased output of monocytes in the pre-metastatic phase and infiltration of macrophages into the pre-metastatic lung. In other words, disturbance of host macroenvironmental homeostasis has influence on future metastatic organs (597).

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, Terkawi and colleagues were unable to confirm these findings for breast cancer surgery. Based on their double blind, placebo-controlled and randomized trial, the authors report that intravenous lidocaine during breast cancer surgery had no effect on opioid consumption, pain score, and postoperative nausea and vomiting (PONV), fatigue and or duration of postoperative hospital stay (598).

However, perioperative lidocaine administration (bolus 1.5 mg/kg at induction, then infusion at 2 mg/hg/hr, up to 2 hours after the end of surgery) was associated with a decreased incidence of post-mastectomy chronic pain. Breast implant and radiotherapy, on the other hand, were associated with an increased incidence of chronic post-surgical pain (CPSP). In this relatively small sample zize (n=61 patients), 20% of the patients developed CPSP (599).

Couceiro et al. have performed a randomized, blinded, placebo controlled trial in which the effects of additional intravenous lidocaine infusion were studied in patients undergoing mastectomy. Their results show that intravenous lidocaine at a dose of 3 mg/kg administered over a period of an hour during mastectomy did not promote additional analgesia, compared to placebo in the first 24 hours. Furthermore, there was also no effect on opioid consumption (600).

Based on the results of their prospective nationwide cohort study, Lefebvre-Kuntz and colleagues report that general anaesthetic agents do not influence persistent pain after breast cancer surgery (601).

Furthermore, it has to be noted that previous studies have shown that amide-linked local anaesthetics display anti-tumour effects (53-61,863). 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 (58).
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 (602).

Interestingly, Liu and colleagues report that cytochrome P450 polymorphism may alter the sensitivity of epidural ropivacaine in patients undergoing breast cancer surgery. Cytochrome P450 (CYP450) is known to metabolize ropivacaine in the liver and to consist of several polymorphisms. In their study, Liu et al. demonstrate that patients with certain CYP450 polymorphisms undergoing mastectomy with axillary lymph node clearance require lower doses of epidural ropivacaine than those with other polymorphisms. Therefore, they

conclude that detection of these specific polymorphisms (rs11636419 AG and GG genotypes, respectively rs17861162 CG and GG genotypes) may aid in the development of effective personalized treatments for breast cancer patients (603).

Mahalingaiah et al. claim that chronic oxidative stress is able to convert oestrogen-dependent non-aggressive breast cancer cells into oestrogen-independent aggressive cells (604).

Finally, Rivero's group concludes that salbutamol could be an effective adjuvant drug for the treatment of metastatic breast cancer. In their laboratory study, both salbutamol (β2-agonist) and propranolol (β-blocker) significantly diminished human breast cancer cell migration while epinephrine exerted opposite effects. Furthermore, salbutamol inhibited invasion of breast cancer cells and enhanced adhesion to extracellular matrix. Salbutamol treatment proved also able to decrease the expression of pro-metastatic genes (605).

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. One study focussed on the effects of high-dose postoperative opioids on cancer recurrence in patients undergoing oesophageal cancer surgery. In this retrospective analysis, high-dose intraoperative and postoperative opioid use (>1783.5 mg of oral morphine) was significantly associated with with an increased risk of oesophageal cancer recurrence. However, opioid use and/or opioid dosage did not affect overall survival (606).

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 (607). 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 (608).

Andreou's group reports that anastomotic leakage following resection for oesophageal and gastric cancer has a negative prognostic impact on long-term survival, independent from tumour stage and biology (609).

Fumagalli et al. claim that intraoperative hypotensive episodes may be associated with postoperative oesophageal anastomotic leakage. In this prospective study, data from 48 patients undergoing oesophagectomy with gastric pull-up were collected. Hypotensive epidodes (defined by systolic pressure decreasing more than 30% of the basal value for more than 5 minutes) were significantly more frequent in patients undergoing prone

oesophagectomy and those with an epidural catheter used during surgery. Anastomotic leaks were significantly more common in patients with intraoperative hypotensive episodes (HEs), especially those treated with vasopressive agents. The authors conclude that the intraoperative use of epidural analgesia can, in certain conditions, significantly influence gastric blood flow due to hypotensive episodes (610). However, it remains questionable whether the higher incidence of anastomotic leaks is a direct result of anastomotic hypoperfusion caused by the vasodilatatory effects of epidural analgesia resulting in hypotension, or the combined result of anastomotic hypoperfusion caused by neuraxial vasodilatation in combination with vasoconstriction at the site of the anastomosis caused by the vasopressors used.

Baker and co-workers report that drain amylase detection within 10 days after oesophagectomy adds to the sensitivity of CT oesophagram in the early detection of anastomotic leakage (611).

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 (612).
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 (613).

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 (614). This retrospective analysis included 153 patients, of whom 118 patients received epidural analgesia. Epidural analgesia was avoided in 35 patients for reasons not mentioned.

Feltracco and colleagues have conducted a clinical review on the benefits of thoracic epidural analgesia in oesophageal surgery and conclude that, although its advantages on

faster mobilization, pulmonary functions and pain control are soundly established, this technique requires specific technical skills and is not devoid of risks, complications, and failures (615).
By contrast, Visser's group claims that thoracic epidural analgesia has no beneficial effects on postoperative pain scores or pulmonary complications compared with systemic analgesia (616).

Based on the results of their meta-analysis of randomized and controlled trial, Hughes and co-workers conclude that thoracic epidural analgesia is not associated wih reduced overall morbidity. Although epidural analgesia was associated with reduced pulmonary complications following gastrectomy, no obvious benefits were encountered following oesophagectomy (617).

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 showed 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 (618).

Li and co-workers also have examined the effects of epidural analgesia on short and long-term outcomes after oesophagectomy and compared these with intravenous analgesia. Results of this propensity-matched cohort study revealed that epidural analgesia could attenuate the surgical inflammatory response and reduce the incidence of pneumonia and anastomotic leakage after oesophagectomy. However, these benefits were at the price of delayed urinary catheter removal and lower blood pressure. The authors conclude that epidural analgesia remains an important component of multimodal perioperative management after oesophagectomy (619).

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 III and I received postoperative patient-controlled intravenous analgesia (PCIA), whilst patients in groups II and IV received PCEA. Levels of cortisol and cytokines were measured in peripheral blood samples collected prior to anaesthesia 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 (620).
These results are in conflict with the previously mentioned study results from Ramirez et al. Based on their results the investigators conclude that the magnitude of innate immune suppression is similar among different oncological procedures (517).

Han and co-workers report that the use of propofol and/or dexmedetomidine as an induction agent results in less oxidative stress compared with the use of midazolam. In their prospective and randomized trial oxidative stress indicators were assessed prior to, and at 2 and 24 hours after oesophageal cancer surgery and radical prostatectomy. The patient group in which midazolam was used for induction of anaesthesia showed significantly higher oxidative stress compared with the propofol and dexmedetomidine group (621). In other

words, propofol and dexmedetomidine are claimed to exhibit a superior antioxidant function.

Jun and colleagues report that volatile anaesthesia is associated with worse overall survival and recurrence-free survival compared with intravenous anaesthesia with propofol (TIVA). In their retrospective observational study, TIVA during oesophageal cancer surgery was associated with better postoperative survival rates compared to volatile anesthesia (622).

Based on the results of their retrospective cohort study, Zhang and Wang conclude that sevoflurane does not differ from propofol in terms of affecting the risk of postoperative pneumonia development after oesophagectomy (623).

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 (624).

Interestingly, Ma et al. claim that thoracoscopic oesophagectomy has some obvious advantages associated with less pulmonary complications, lower morbidity of injury to the thoracic duct and recurrent laryngeal nerve. However, compared to open oesophagectomy thoracoscopic intervention was not associated with reduced surgical stress response (625).

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 (254). However, the results of their observational cohort study show that aspirin and other NSAIDs presciptions after diagnosis are associated with reduced all-cause mortality in UADT cancer patients (255).

By contrast, Thrift's group failed to demonstrate a positive association between the use of NSAIDs and a reduced risk of Barrett's oesophagus (626).

Hu et al. report that COX-2 expression level is asscociated with key clinicopathological features and could be an effective biomarker to predict prognosis following Ivor Lewis oesophagectomy in patients with oesophageal squamous cell carcinoma (627).

Van Staalduinen and colleagues demonstrate that postdiagnosis aspirin use might be associated with a higher survival rate in oesophageal cancer patients. However, postdiagnosis NSAIDs use was not associated with higher survival rate in this group of patients (628).

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 (151).
Yuan and colleagues report similar findings. 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 (629).

Xiao et al. confirm that preoperative NLR is a prognostic biomarker in patients with basaloid squamous cell carcinoma of the oesophagus undergoing curative surgery (630).

Grenader and colleagues also confirm that NLR may predict the presence of peritoneal or metastatic involvement on staging laparoscopy, in patients with early lower oesophageal cancer or gastric cancer. A high NLR (≥ 3.28) was significantly associated with positive peritoneal and/or metastatic disease at staging laparoscopy (631).

Yoo et al. have studied the association between NLR and survival after chemo radiotherapy for locally advanced oesophageal cancer. In their study, low pre-treatment NLR (< 2.0) was clearly associated with longer progression-free and overall survival compared with the high NLR (≥ 2.0) group (632).

Li and co-workers confirm the prognostic significance of pre-chemotherapy NLR in patients undergoing radical oesophagectomy for locally advanced oesophageal squamous cell cancer. Their study results show that a pre-chemotherapy 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) (633).

Sürücü et al. even claim that baseline NLR is associated with the metabolic tumour volume in patients with oesophageal cancer (634).
Yutong and colleagues confirm the prognostic significance of NLR for oesophageal cancer in high incidence areas in China. A high NLR (≥ 3.5) was significantly associated with shorter overall survival compared to a low NLR (< 3.0) (635).

He and co-workers report that elevated NLR and PLR might be used as predictive factors in patients with middle or lower oesophageal squamous cell carcinoma. In their retrospective study, high NLR (> 3.3) was significantly associated with worse overall survival. PLR > 150, on the other hand, was significantly associated with worse disease-free survival (636).

By contrast, Hirahara et al. state that platelet-to-lymphocyte ratio (PLR) can be used as a novel predictor of postoperative cancer-specific survival and overall survival in patients with oesophageal cancer. The authors also state that PLR may be useful in identifying patients with a poor prognosis even after radical oesophagectomy (637).

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 (638).

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 (639).

On the other hand, Yodying and co-workers report that based on the results of their meta-analysis, both high NLR and high PLR were significantly predictive of poorer overall survival in patients with oesophageal cancer. However, high PLR but not NLR was significantly predictive of poorer overall survival in patients who underwent curative surgery without neoadjuvant chemotherapy (640).

By contrast, Jung et al. claim that a high NLR (≥ 2.97) is a significant prognostic factor for overall survival and disease-free survival in patients with surgically treated oesophageal squamous cell carcinoma. In this retrospective study, elevated PLR was not a risk factor for overall and disease-free survival (641).

Hyder’s group demonstrates that changes in NLR and PLR during chemoradiation predict survival and pathologic complete response in oesophageal cancer patients undergoing trimodality therapy (642).

Kijima et al. have investigated the predictive effects of NLR and plasma fibrinogen in patients with advanced oesophageal cancer. Furthermore, they assessed the clinical utility of a combined score using NLR and plasma fibrinogen, named F-NLR, as a predictor of

tumour response and prognosis. A group of 98 patients with advanced oesophageal squamous cell cancer treated with chemoradiotherapy or chemotherapy, were classified into one of three groups: F-NLR score of 2, having both hyperfibrinogenaemia (> 400 mg/dl) and high NLR (> 3.0); F-NLR score of 1, having one of these two haematological abnormalities, and F-NLR score 0, having neither hyperfibrinogenaemia nor high NLR. Results showed significantly lower overall survival in patients with F-NLR score 2 compared with patients with a F-NLR score of 0 or 1. Therefore, the authors conclude that the F-NLR score is promising as a predictive marker for therapeutic effects and prognosis in patients with with advanced oesophageal squamous cell carcinoma (643).

Matsuda and colleagues report that an intense postoperative inflammatory response (IIR), defined as a delayed C-reactive protein (CRP) level peak and persistent CRP elevation following transthoracic oesophagectomy, is a significantly independent predictive factor for overall survival. Patients with a IIR showed a significantly shorter overall survival (644).

As mentioned previously in the case of head and neck cancers, Chang and co-workers state that, based on the results of their population-based cohort study, propranolol might reduce the risk of head and neck, oesophagus, stomach, colon and prostate cancers (275).

Finally, Horikoshi's group has conducted a randomized, controlled trial in which the effects of landiolol administration on the occurrence of postoperative atrial fibrillation and tachycardia in patients undergoing oesophageal surgery were investigated. Their results show that administration of 5µg/kg/min of the cardioselective ultra-short acting β-blocker landiolol results in significantly lower incidence of atrial fibrillation and sinus tachycardia in patients underging oesophagectomy. Furthermore, IL-6 levels at the end of surgery were also significantly lower in the landilol group, suggesting a possible reduction in the surgical stress response (645).

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 (117). A finding previously encountered in the case of breast cancer and lung cancer.

Bameshki and co-workers have performed a randomized, double blinded trial in which the effects of additional paracetamol and/or diclofenac to patient-controlled morphine analgesia for postgastrectomy pain control were investigated. Their results show that intravenous paracetamol or diclofenac suppositories decrease morphine consumption by almost 32% and also improve alertness (646).

Shen et al. have studied the effects of the non-steroidal anti-inflammatory drug flurbiprofen on immune function in gastric cancer patients receiving postoperative morphine analgesia. Based on the results of their prospective, randomized study they conclude that the combination of morphine and flurbiprofen ameliorates the immune depression in T-lymphocyte subsets and natural killer cells and provides a similar analgesic efficacy to morphine alone. Interestingly, T-lymphocyte depression lasted for 120 hours after surgery (647).
Sun and colleagues report similar findings. Based on their prospective, randomized study they conclude that patient-controlled intravenous analgesia (PCIA) using tramadol combined with the non-steroidal anti-inflammatory drug lornoxicam has less influence on inflammatory cytokines than morphine or tramadol alone in patients undergoing gastric cancer surgery (648).
Both study results endorse the importance of anti-inflammatory drugs in the preservation of immunity following surgery.

Jiang et al. have performed a prospective, randomized study in which the effects of type of anaesthesia on the stress response were examined in patients undergoing laparoscopic radical gastrectomy. One hundred patients were randomized into either the total intravenous anaesthesia (TIVA) group, or the combined intravenous and inhaled anaesthesia (CIIA) group. TIVA was performed with propofol and remifentanil by means of target-controlled

infusion. CIIA was performed by inhalation of sevoflurane and continuous infusion of remifentanil after anaesthesia induction. Concentrations of epinephrine, norepinephrine and dopamine in plasma from radial artery blood samples were measured at different time intervals. Results revealed that, at the same anaesthetic depth, the CIIA method outperformed the TIVA method in suppressing the stress response and obtaining smooth awakening after laparoscopic radical gastrectomy for patients with gastric cancer (649).

Yon and co-workers demonstrate in their prospective, randomized, double-blinded 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. 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 (650).

Kang cum suis report comparable results showing that intraoperative intravenous lidocaine reduces opioid consumption and hospital length of hospital stay following open gastrectomy for stomach cancer in men. In this prospective, randomized, double-blinded trial, 48 patients were randomly allocated into two groups. One group received intravenous lidocaine 1.5 mg/kg 20 minutes before incision followed by a continuous lidocaine infusion of 1.5 mg/kg/hr until the end of surgery. The control group received saline in a similar manner. Results showed no differences in total consumption of iv-controlled analgesia or pain scores at 24, 48, or 72 hours postoperatively. Also, no differences were noted between both groups in pain intensity or duration of ileus. However, patients in the lidocaine group had significantly decreased average supplemental pethidine requirement per patient for pain control until 72 hours postoperatively and hospital length of stay (651).

Based on the results of their prospective, randomized, double blind and placebo-controlled study, Kim et al. confirm that pre- and intraoperative lidocaine reduces the consumption of opioids in patients undergoing laparoscopy-assisted distal gastrectomy (652).

Kim and colleagues claim that intravenous lidocaine infusion is a safe sedative method during endoscopic submucosal dissection for gastric neoplasms. In their randomized, double-blinded study, adjuvant intravenous lidocaine infusion resulted in reduced opioid requirement and decreased patient movement during this procedure (653).

Based on the results of their comparative meta-analysis, Khan and co-workers claim that the continuation of intravenous lidocaine infusion beyond 60 minutes after bowel surgery has no added analgesic or gastrointestinal benefit (654).

As mentioned previously in the case of breast cancer, lidocaine has been shown to demethylate DNA in breast cancer cells, and by doing so lidocaine sensitizing the cytotoxicity of cisplatin (602).
Xing's group confirms the antitumour activity of intravenous lidocaine in hepatocellular carcinoma. Furthermore, the authors state that combining lidocaine with cisplatin may be a novel treatment option for hepatocellular carcinoma (655).
Jurj et al. conclude that in clinically relevant concentrations, lidocaine displays significant antiproliferative effects on human hepatocarcinoma cells. These effects are time and dose-dependent (656).

However, Ortiz et al. state that intravenous lidocaine was not able to reduce postoperative pain, opioid consumption, and duration of ileus or length of hospital stay in patients undergoing laparoscopic cholecystectomy. This conclusion is based on the results of their prospective, randomized, double-blinded study (657).

Dale and co-workers also have prospectively studied the analgesic efficacy of intravenous lidocaine infusion in patients undergoing laparoscopic fundoplication. In fact, this study was terminated after an interim analysis showing evidence of futility. There was no difference in postoperative pain scores at rest or with movement. In this study, patients in the lidocaine group received 1 mg/kg intravenous bolus prior to induction of anaesthesia, followed by an intravenous infusion at 2 mg/kg/hr for 24 hours (658).

Kranke and colleagues have performed a meta-analysis in which the effects of perioperative intravenous lidocaine infusion on postoperative pain and recovery in adults undergoing various surgical procedures were studied. The authors conclude that there is low to moderate evidence that perioperative continuous intravenous infusion of lidocaine, when compared to placebo, has an impact on pain scores and/or postoperative nausea. Furthermore, there is limited evidence that this intervention has further impact on other relevant clinical outcomes, such as gastrointestinal recovery, length of hospital stay, and opioid requirements (659).

As mentioned earlier in the case of lidocaine, procaine is also reported to act as a specific DNA methylation inhibitor for human gastric cancer cells. By repressing DNA-methylation levels proliferation arrest and apoptosis of gastric cancer cells are promoted (660).

Based on the results of their prospective, randomized trial, Kuo et al. report that thoracic epidural analgesia (with lidocaine) results in better pain relief, lower opioid consumption, earlier return of bowel function, and lesser production of cytokines than intravenous lidocaine during 72 hours after colonic surgery (661).

Li and co-workers state that when used in conjunction with TIVA, intraoperative dexmedetomidine attenuates surgical stress responses to an extent comparable to combined epidural and general anaesthesia without compromising hemodynamic stability and with minimal effects during the intraoperative period. In this prospective study, patients in the demedetomidine group received dexmedetomidine 0.6 µg/kg intravenously before induction of general anaesthesia, followed by dexmedetomidine 0.4 µg/kg/h until peritoneal closure. The control group received volume-matched normal saline infusion as placebo. The epidural group received epidural anaesthesia with 0.375% ropivacaine combined with TIVA (662).

Dong et al. confirm that the intraoperative use dexmedetomidine can effectively reduce the release of inflammatory cytokines in patients undergoing gastric cancer surgery. In their randomized study, patients in the dexmedetomidine group received 1 µg/kg as a bolus, followed by a continuous infusion of 0.2 µg/kg/hour till the end of operation. Patients in the control group received the same volume of saline. In both groups, the levels of pro-

inflammatory cytokines were significantly elevated compared with the levels prior to incision. However, the elevation was significantly higher in the control group compared to the dexmedetomidine group (663).

Kim and colleagues report similar results. In their randomized study, patients were allocated into 1 of 3 groups: conventional thoracic epidural PCA (E-PCA); dexmedetomidine in combination with fentanyl-based intravenous-PCA (dIV-PCA); fentanyl-based IV-PCA only (IV-PCA). Their results showed that dexmedetomidine in combination with fentanyl-based IV-PCA significantly improved postoperative analgesia in patients undergonig open gastrectomy without hemodynamic instability, which was comparable to thoracic E-PCA. According to the authors, this approach could be clinically more meaningful owing to its non-invasive nature (664).

Yanagimoto and co-workers have studied the optimal analgesia following laparoscopic distal gastrectomy and evaluated the effectiveness of epidural analgesia for this type of surgery. Based on the results of their retrospective study, they conclude that epidural analgesia results in significantly earlier bowel movements and less need for additional opioids. However, epidural analgesia did increase the risk of urinary retention (665).

Zhang et al. have investigated the awakening (quality and time) of elderly patients from propofol intravenous general anaesthesia or sevoflurane inhalation general anaesthesia combined with epidural analgesia after radical gastric cancer surgery. Their results show that, compared to propofol intravenous general anaesthesia or sevoflurane inhalational general anaesthesia, propofol or sevoflurane general anaesthesia combined with epidural analgesia was more conducive to increase the awakening quality of elderly patients from anaesthesia following radical gastric cancer surgery (666).

Based on the results of their retrospective analysis, Wang et al. report that general anaesthesia combined with epidural analgesia may be associated with improved survival in gastric cancer patients undergoing resection. Furthermore, pain scores and the incidence of nausea and vomiting were significantly lower in the general anaesthesia combined with epidural analgesia group than in the general anaesthesia alone group (667).

By contrast, Shin's group reports that *postoperative* use of epidural analgesia is not associated with reduced recurrence or mortality following gastric cancer surgery (668). Obviously, more prospective study results on this topic are needed.

With respect to gastric cancer surgery, Long et al. conclude that radical surgery dramatically upregulates the expression of pro-tumourigenic cytokines in the peritoneum. Furthermore, there is a marked systemic immune and inflammatory response to surgery, including the downregulation of T-cell and dendritic cell populations. According to the authors, tumour progression may be facilitated via two potential pathways: local inflammation promoting peritoneal adherence and implantation, and secondary suppression of immunosurveillance due to circulating inflammatory response (669).

Ganapathi and colleagues report that epidural analgesia is safe and effective in providing adequate pain relief following open liver surgery. They base this conclusion on the results of their study in which 70 patients undergoing open liver surgery were included. Epidural analgesia was reported successful in 64 patients (91%). Bacterial colonisation of the epidural tip was noticed in two patients, without neurological complications. Five patients (7%) had radiologically confirmed chest infection, and four patients (6%) developed wound infection. The median length of stay was 6 days (3-27 days). The extent of liver resection and postoperative chest infection had a significant influence on the length of stay (670).

Zhu et al. have conducted a prospective, randomized, controlled trial in which the effects of combined epidural analgesia and general anaesthesia were investigated on intraoperative hemodynamic responses, postoperative cellular immunity, and prognosis in patients undergoing surgery for gallbladder cancer. Their results show that combined epidural analgesia and general anaesthesia results in less PONV, better pain scores, and improved postoperative cellular immunity when compared to general anaesthesia alone. The 1-year, 2-year, and 3-year survival rates, however, were not evidently different between both groups. Therefore, the authors conclude that combined epidural analgesia and general anaesthesia might be a more available anaesthesia method for gallbladder cancer patients undergoing surgery (671).

Based on the results of their randomized controlled trial, Aloia's group states that thoracic epidural analgesia provides superior patient experience through improved pain control and less narcotic use in patients underoing major hepatopancreatobiliary surgery, without increasing length of stay or complications (672).

Joy and co-workers demonstrate that epidural ropivacaine with dexmedetonidine significantly reduces the total propofol dose required for induction of anaesthesia in patients undergoing abdominal and lower extremity surgery. Furthermore, this combination decreases the onset time of sensory and motor block and provides good haemodynamic stability (673).

Meanwhile, Misquith and colleagues report that thoracic epidural analgesia provides superior analgesia, better cough reflex (as seen by better peak expiratory flow rates), more haemodynamic stability and better ventilation in patients undergoing upper abdominal surgery (674).

Schreiber's group has performed a randomized, prospective, open label study in which epidural analgesia was compared with bilateral paravertebral nerve blockade (PVB) in patients undergoing open liver resections. Results showed significantly lower pain scores in the epidural group at 24 and 48 hours postoperatively compared with the bilateral PVB group. However, there was also a significant decrease in mean arterial pressure from baseline at 24 hours postoperatively in the epidural group. Maximal inspired ventilatory volumes at 24 hours postoperatively and cumulative utilization patient-controlled analgesia opioid during the first 48 hours postoperatively did not significantly differ between the two groups (675).

Based on the results of their prospective and randomized study, Xu et al. conclude that general anaesthesia combined with epidural block has little passive influence on the cellular immunity of the body and therefore can be selected as an anesthetic approach for patients with liver cancer (676).

Allen and colleagues have retrospectively investigated the analgesic effects of epidural analgesia and compared these with patient-controlled analgesia in patients undergoing liver resections for neoplastic disease. Their results show that overall postoperative outcomes (time to ambulation and complications) were not significantly different based on method of analgesia after adjusting for type and extent of hepatic resection. However, although patients with epidural analgesia underwent more extensive surgeries they required less additional intravenous pain medications than patients with intravenous patient-controlled analgesia (677).

As mentioned previously, Shah's group states that intraoperative continuous epidural infusions decrease PACU length of stay as discharge criteria for patient-reported pain scores are met earlier (306).

Wang (J.) and co-workers have retrospectively investigated the effects of additional epidural analgesia on the long-term survival in gastric cancer patients. Results revealed no obvious association between epidural use and improved long-term survival. However, epidural analgesia was significantly associated with improved long-term survival among younger patients (age up to 64 years), but not among older patients (678).

By contrast, Wang (M.) et al. report that epidural anaesthesia combined with general anaesthesia and patient-controlled epidural analgesia may be associated with improved overall survival in gastric cancer patients undergoing resection. In this retrospective study, intra- and postoperative epidural use was significantly associated with improved survival (679).

Amini et al. have performed a nationwide retrospective cohort study in which the effects of perioperative thoracic epidural analgesia in patients undergoing hepatopancreatic surgeries were examined. They conclude that epidural analgesia use among these patients remains low (overall 7.4%). Albeit, epidural analgesia was associated with a reduction in specific pulmonary-related complications, as well as in-hospital mortality (680).

Sugimoto and colleagues claim that outcomes after pancreatic resection can be improved by increasing the success rate of epidural anaesthesia. This claim is based on the results of their retrospective study in which the association between epidural dysfunction and surgical outcomes was investigated. Epidural dysfunction was defined as either hypo-function due to inadequate pain control (requirement of epidural replacement, conversion to intravenous continuous opioid infusion, or intravenous bolus opioid use) or hyper-function (hypotension or oliguria). Epidural dysfunction was reported to occur in 49% after pancreatectomy (hypo-function in 35% and hyper-function in 14%). Epidural dysfunction was independently associated with the development of overall, pancreas-related, and non-pancreas-related complications. Hypo-function alone was independently associated with both pancreas-related and non-pancreas-related complications. Hyper-function, on the other hand, was independently associated with non-pancreas-related complications (681).
These results emphasize the importance of adequate epidural anaesthesia. It should be stressed that active management of inadequate epidural anaesthesia, including a new block, may result in an almost complete success rate (682).
For a more comprehensive overview of epidural dysfunction we refer to the article published by Hermanides et al. (683).

In turn, Sadowski and co-workers have performed a prospective and randomized study in which the effects of epidural analgesia/anaesthesia on pancreatic perfusion in patients with acute pancreatitis were examined. Their results demonstrate that epidural analgesia increases arterial perfusion of the pancreas and improves the clinical outcome of patients with acute pancreatitis. In this study, mean duration of epidural analgesia was 5.7 days and no complications of the epidural procedure were reported (684).
Jabaudon’s group supports these findings. In their multicentre, observationl cohort study, mortality at 30 days was significantly lower in critically ill patients with acute pancreatitis who received epidural analgesia compared with patients without epidural analgesia (685).

Kun et al. have investigated the effect of combined general anaesthesia with epidural analgesia on postoperative NK-cell activity and cytokine response in gastric cancer patients undergoing radical resection. In their prospective study, patients were randomized to combined general/epidural anaesthesia or general anaesthesia alone. Natural killer cell

activity and serum concentrations of pro-tumourigenic cytokines (IL-1β and IL-6), and anti-tumorigenic cytokines (IL-2 and IL-10) were measured at different time intervals. Results revealed a significantly less decreased NK-cell activity in the epidural group, higher levels of anti-tumourigenic cytokines and lower levels of pro-tumourigenic cytokines. Therefore, the authors conclude that combined general/epidural anaesthesia seems helpful to maintain the body's perioperative immune function compared to general anaesthesia alone in patients with gastric cancer surgery (686).

This conclusion is supported by the results of a prospective randomized study performed by Zhao and Mo. In this study, the effects of epidural analgesia were investigated in patients undergoing surgery for gastric cancer. The patient group that received general anaesthesia with continuous epidural analgesia had significantly lower contents of TNF-α, IL-6, and IL-8. Furthermore, the number of T-lymphocytes and NK-cells was significantly lower in the patient group that received general anaesthesia without epidural analgesia. Seventy-two hours after the operation, the number of T-lymphocyte subsets and NK-cells were back to normal, but still significantly lower than before the operation and anaesthesia in the general anaesthesia alone group. According to the authors, this illustrates that general anaesthesia with continuous epidural analgesia is a more preferred anaesthetic technique for gastric cancer patients undergoing surgery. The surgical stress response is attenuated and consequently the immune function is less suppressed (687).

Kasai and colleagues claim that the surgical stress response following laparoscopic and open liver resection for colorectal liver metastasis is comparable. In this prospective trial, patients were randomized to receive open or laparoscopic liver resection. Apart from a shorter postoperative stay in the laparoscopic group, there were no significant differences between both groups with respect to the levels of IL-6, IL-8, and the levels of angiogenesis-related factors and inflammation-related factors (688).

By contrast, Okholm et al. have studied the inflammatory stress response in laparoscopic versus open surgery for gastric cancer. Based on the results of their meta-analysis, they conclude that laparoscopy-assisted gastric surgery attenuates the immune response compared to open surgery. Especially IL-6 and CRP plasma concentrations were

significantly lower in laparoscopic patients compared to patienst undergoing laparotomy (689).
Consequently, a laparoscopy proves to be less immunosuppressive than a laparotomy (7). Bartin and Schietroma et al. confirm this finding, even in the case of generalized peritonitis from perforated appendicitis (690,691).

Freise and colleagues report that thoracic epidural analgesia (TEA) reduces liver injury in necrotizing acute pancreatitis. In their study, TEA significantly reduced liver injury in rats with induced necrotizing pancreatitis. Therefore, the authors conclude that TEA could preserve liver function in systemic inflammatory disorders such as acute pancreatitis (692). Furthermore, the same group also reports that TEA reverses sepsis-induced hepatic hyperperfusion and reduces leucocyte adhesion in septic rats (693).

With respect to acute pancreatitis, and based on the results of their laboratory study, Barlass and co-workers claim that morphine treatment worsens the severity of acute pancreatitis and delays resolution and regeneration. Therefore, the authors conclude that the safety of morphine for analgesia during acute pancreatitis shoul be re-evaluated in future human studies (694).

Sidiropolou et al. have performed a randomized, double blind trial in which the impact of anaesthetic technique on the stress response elicited by laparoscopic cholecystectomy was investigated. Their results show that hormonal and metabolic stress response is slightly modulated by the use of epidural analgesia supplemented by general anaesthesia (695).
In this study, blood markers were determined 1 day before surgery, intraoperatively, and upon the first postoperative day.

Ozcan and co-workers also have investigated the effects of thoracic epidural analgesia on cytokine response in patients undergoing laparoscopic cholecystectomy. In this prospective, randomized comparative study, 60 adult patients scheduled for elective laparoscopic cholecystectomy were included and a thoracic epidural catheter was inserted before incision. Patients were divided into 4 groups. Group saline (group S), group fentanyl (group F), group bupivacaine (group B), and group levobupivacaine (group L). Patients in group S

received saline, patients in group F fentanyl, in group B bupivacaine, and patients in group L levobupivacaine via the epidural catheter. In all groups, interleukin-6 (IL-6), IL-8, and IL-10 started to increase at 2 hours after incision and returned to the basal level at 24 hours after surgery. Interleukin levels increased most in patients who had received saline via the epidural catheter. Therefore, the authors conclude that combined general anaesthesia and thoracic epidural analgesia provide pain control and hemodynamic stability more efficiently during the first 24 hours of the intraoperative and postoperative period by suppressing cytokine levels (696).

In their paper, Gottschalk and Poepping summarize the current knowledge on the effects of epidural analgesia on pain management, the cardiopulmonary and gastrointestinal systems, and patient's outcome (697).

Remarkably, Aspinen and colleagues report that the concentrations of oxidative stress markers following minilaparotomy cholecystectomy and laparoscopic cholecystectomy are comparable. Apparently, laparoscopic cholecystectomy evokes the same level of stress response as a minilaparotomy (698). This might be attributed to the creation of pneumoperitoneum, which has been shown to result in an increased stress response (905-907,910).
As mentioned previously, Kasai and colleagues report similar results in patients undergoing laparoscopic and open liver resection for colorectal liver metastasis. Apart from a shorter postoperative stay in the laparoscopic group, there were no significant differences between both groups with respect to the levels of inflammatory cytokines and the levels of angiogenesis-related factors and inflammation-related factors (688).

Sen et al. have prospectively investigated the effects of pressure-controlled (PCV) and volume-controlled (VCV) ventilation on respiratory mechanics and systemic stress response during laparoscopic cholecystectomy. Their results show that PCV improved compliance during pneumoperitoneum, improved oxygenation, and reduced stress response postoperatively compared with volume-controlled ventilation (699).

Kadam's group reports that the performance of TAP block with respect to pain management is comparable to local infiltration in patients undergoing day surgery laparoscopic cholecystectomy (700).

Sinha et al. claim that ultrasound-guided TAP block with ropivacaine (0.375%) provides better effective analgesia in the immediate postoperative period up to 1 hour as compared to bupivacaine (0.25%). However, there were no differences between both drugs with respect to postoperative analgesia and 24 hour cumulative analgesic requirement (701).

Based on the results of their prospective, single blinded and randomized trial, Al-Refaey et al. report that adding magnesium sulphate to bupivacaine in TAB blockade during anaesthesia for laparoscopic cholecystectomy improves postoperative analgesia by increasing its duration, decreasing the analgesic requirements, and decreasing PONV (702).

Interestingly, Kim (YS) and colleagues point out that the short acting beta-blocker esmolol plays 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 (703).

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 (704).

Consequently, Takahashi's group confirms that β2-adrenergic receptor expression is a significant predictor of tumour aggressiveness in, and poorer survival of, patients with gastric acncer (705).

Pu et al. claim report that epinephrine promotes epithelial-to-mesenchymal transition in pancreatic cancer cells (706).

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 (707).
This claim is supported by Yagi's group. They have examined the anti-tumour effects of a combination of sorafenib, a multi-target oral anti-neoplastic drug, and COX inhibitors on hepatocellular carcinoma cells. Their results clearly show that co-administration of COX inhibitors and sorafenib increases the frequency of apoptosis (708).

Hang et al. report that COX-2 inhibitors have the ability to inhibit angiogenesis and metastasis of pancreatic ductal adenocarcinoma via the suppression of specificity protein 1 (Sp1). Also, COX-2 and Sp1 expression proved positively correlated with a poor prognosis in pancreatic ductal adenocarcinoma (709).

By contrast, Khalaf and co-workers report that, based on the results of two large cohort studies, regular aspirin or non-aspirin NSAID use is not associated with lower risk of pancreatic cancer. However, they state a possible reduction in risk for pancreatic cancer among people with diabetes mellitus who use aspirin should be further examined in preclinical and human studies (710).

In addition, Bombardo et al. caution against prolonged use of ibuprofen and diclofenac treatment in patients with acute pancreatitis. In their study on mice, therapeutic ibuprofen and diclofenac treatment inhibited pancreatic acinar cell division. According to the authors, this finding suggests that prolonged treatment with these NDAIDs might negatively affect the regeneration of the pancreas (711).

Based on the results of their population-based case-control study, Kho and colleagues conclude that the use of NSAIDs or statins may reduce the odds of developping pancreatic cancer. However, there was no true consistent evidence of an association between NSAIDs

or statins use and risk of pancreatic cancer. There was some suggestion of a prospective effect in infrequent users of selective COX-2 inhibitors, but no association in more frequent users (712).

Petrick and co-workers have harmonized data on over a million individuals from ten prospective cohort studies in order to investigate the relation between NSAID use and the risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Their results show that current aspirin use, versus non-use, was inversely associated with hepatocellular carcinoma (HCC). This association was stronger for users who reported daily use, longer duration use, and lower dosage. Ibupriofen was not associated with HCC risk. As far as intrahepatic cholangiocarcinoma is concerned (ICC), aspirin use was associated with a reduced risk in men, but not women. The authors conclude that the observed inverse association between aspirin use and liver cancer in this study merits further intervention studies of aspirin and other agents that affect chronic inflammatory pathways for HCC and possibly ICC (713).

Based on the results of their prospective cohort study, Vaughan and colleagues conclude that aspirin use may prevent incident pancreatic, breast, colon, and ovarian cancer in elderly women (414).

As mentioned previously, Zhang et al. have demonstrated that propofol exhibits anti-tumour effects by inhibiting growth of human hepatocellular cancer cells (25).

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 (578).

Boas and colleagues have retrospectively investigated the effects of β-blocker and aspirin use on mortality in patients undergoing embolization for hepatocellular carcinoma. Their

results show that aspirin and β-blocker use is associated with significantly improved survival when taken at the time of embolization (714).

However, in their nested-case control study Hagberg and co-workers failed to detect an association between the use of angiotensin-converting enzyme (ACE) inhibitors and/or β-blockers in patients with hypertension and a reduced risk of primary liver cancer (715).

Li and colleagues claim that expression of monoamine oxidase A (MAOA), a catecholamine neurotransmitter degrading enzyme, is closely related to cancer vaso-invasion, 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 (716).

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 (183-187). Strikingly, the tumour-enhancing effects of S-ketamine could largely be undone by administering beta-blockade.

Huan and co-workers claim that sympathetic innervation is crucial for hepatocarcinogenesis and that the sympathetic nervous system promotes hepatocarcinogenesis by activating α1-adrenergic receptors of Kupffer cells to boost the activation of Kupffer cells and to maintain the inflammatory microenvironment. Hence, the authors conclude that these findings indicate that sympathetic denervation or α1-adrenergic receptors blockage may represent novel tretmant approaches for hepatocellular carcinoma (717). Consequently, this might explain why neuraxial analgesia, by blocking the sysmpathetic nervous system, is increasingly reported to have favourable effects on reducing tumour growth and metastasis.

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 therapies 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 (718).

Based on the results of their retrospective study, Beg's group concludes that the use of β-blockers, heparin, insulin, and warfarin is associated with improved survival in patients with pancreatic cancer. The use of metformin, thiazolidinedione, statin, and combination of therapies was not (719).

Partecke and co-workers report similar results. In their orthotopic and syngeneic model of pancreatic cancer, β-catecholamines increased proliferation and migration of cancer cells, whereas propranolol reduced these effects by 25%. When stressed tumour-bearing animals were treated with propranolol tumour volumes were reduced by 69% and survival improved by 14% (720).

Anker and colleagues have investigated the effects of resting heart rate on survival in cancer patients. In their prospective cardiovascular study, resting heart rate (independently of haemoglobin and tumour stage) was shown to predict survival in patients with advanced pancreatic cancer, non-small-cell lung cancer, and colorectal cancer (391).

As mentioned previously, Malsy and colleagues report that both ketamine and S-ketamine inhibit proliferation and apoptosis in pancreatic cancer cells (190).

Based on the results of their cohort study, Udumyan and co-workers state that β-blockers may improve survival of pancreatic ductal adenocarcinoma patients, particularly those with localized disease (721).

In their review, Hefner et al. expand further on the role of stress, β-adrenergic signalling and pancreatic carcinoma (722).
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 (723).

Takahashi and co-workers report that β2-adrenergic receptor expression is a significant predictor of tumour aggressiveness in patients with gastric cancer. Furthermore, β2-adrenergic receptor expression was also associated with poorer survival (724).

As mentioned previously, Lin's study results indicate that long-term treatment with the β-blocker carvedilol is associated with reduced lung and gastric cancer risk (384).

As discussed in the case of lung cancer, epithelial-mesenchymal transition (EMT) is a crucial event responsible for cancer cell invasion and metastasis (86).
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 (725).

The aforementioned findings suggest that stimulation of the beta-adrenergic system could 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 tumour growth.

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 (726).

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 (22).

Interestingly, Cao and colleagues report in their 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 (727).
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 (728). On the one hand, surgical stress response and immunosuppression might not have been attenuated, on the other hand possible pre-emptive mechanisms might have been abolished (79,302).
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 (99,100), opioids in general and morphine in particular have been shown to affect immunity adversely (17,71,72,77,79,84,85,1100).

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 (105). 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 (106).
All of the abovementioned factors could very well have contributed to the difference in findings reported.

Wang and co-workers demonstrate that the addition of epidural analgesia to general anaesthesia improves antitumour activity of T-helper cells in patients undergoing liver cancer resection (729).

Song et al. have performed a meta-analysis of randomized controlled trials in which the effects of the enhanced recovery after surgery (ERAS) program in liver surgery on postoperative recovery were investigated. Epidural analgesia was included in the ERAS program. Overall morbidity, primary length of stay, time of functional recovery, and time to first flatus were significantly shortened in the ERAS group. Quality of life was also better in the ERAS group. However, no significant differences were noted in mortality, readmission rates, operative time and intraoperative blood loss (730).

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 (731).

Dalmau et al. have conducted a double-blind, randomized, controlled trial in which the analgesic effects of continuous wound infusion of local anaesthetic in patients undergoing hepatectomy were investigated. Compared to continuous wound infusion with saline, wound infusion with local anaesthetic did not reduce morphine consumption, nor did it enhance recovery in patients undergoing hepatectomy (732).

However, Mungroop and co-workers suggest that continuous wound infiltration is not inferior to epidural analgesia in hepato-pancreato-biliary surgery within an enhanced recovery setting (733).

In contrast with their previous study on colorectal cancer (836), Cummings et al. were unable to demonstrate an association between epidural analgesia and mortality in patients undergoing resection for gastric cancer (734). 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.

Zimmitti et al. have performed a retrospective study in which the impact of epidural analgesia on oncological outcomes was studied in patients undergoing resection of colorectal liver metastases. Compared to patients who received intravenous analgesia, patients in the epidural group received more intraoperative fluids, had higher urine output volumes, and improved recurrence-free, but not overall survival (735).

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 (736).

Lee and co-workers claim that the administration of a single-dose of intravenous dexamethasone in patients undergoing endoscopic sub mucosal dissection for gastric cancer effectively reduces epigastric pain 6 hours postoperatively. 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) (737).

Ruiz-Tovar and colleagues have compared isolated intravenous opioid analgesia with epidural analgesia and port-sites infiltration with bupivacaine, associated with intravenous analgesia, in patients undergoing laparoscopic sleeve gastrectomy. Their results show that epidural analgesia and port-sites infiltration with bupivacaine, associated with intravenous analgesia, reduce postoperative pain, when compared with intravenous analgesia exclusively (738).

Mohamed et al. have studied the effects of dexmedetomidine, administered intrathecally, 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. Furthermore, the addition of intrathecal fentanyl 25 µg has no valuable clinical effect (739).

Wu and colleagues confirm these results 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 (740).

Moro's group has conducted a randomized, double-blind, placebo-controlled trial in which the effects of ketamine on the quality of recovery following laparoscopic cholecystectomy were investigated. Their results show that intravenous ketamine administration prior to incision, in a dosage of 0.2 mg/kg or 0.4 mg/kg immediately following the induction of anaesthesia, does not improve the quality of recovery following remifentanil-based anaesthesia for laparoscopic cholecystectomy. Furthermore, the incidence of nausea, vomiting, and other complications was also unaffected by ketamine (741).

Bakan et al. claim that opioid-free anaesthesia with dexmedetomidine, lidocaine and propofol infusions may be an alternative technique for laparoscopic cholecystectomy, especially in patients with high risk for postoperative nausea and vomiting. This claim is based on the results of their randomized, double-blind trial in which patients were randomly allocated to receive either opioid-free anaesthesia (with dexmedetomidine, lidocaine and propofol) or opioid-based anaesthesia (with remifentanil and propofol infusions). During anaesthesia, there were more hypertensive events in the opioid-free group compared to the opioid-based group. Patients in the opioid-free group also had significantly lower pain scores, and lower rescue analgesic and anti-emetic need. However, recovery times were significantly higher in the opioid-free group (742).

With respect to intravenous lidocaine infusion, Song et al. state that perioperative systemic lidocaine improves postoperative recovery and attenuates the initiation of excessive inflammatory response following laparoscopic cholecystectomy. In this randomized, controlled trial, intravenous infusion of lidocaine (bolus injection of 1.5 mg/kg at induction of anaesthesia, followed by a continuous injection of 2 mg/kg/hr until the end of surgery) significantly reduced pain intensity at 2 and 6 hours postoperatively, and total opioid consumption 24 hours after surgery when compared with placebo infusion. Time to first flatus passage and time to first bowel movement were also significantly shorter in patients who received intravenous lidocaine. Furthermore, Cytokine release was also reduced in patients treated with intravenous lidocaine (743).

Das and Deshpande have investigated the effects of intraperitoneal bupivacaine and ropivacaine versus placebo on postoperative pain following laparoscopic cholecystectomy.

Based on the results of their randomized, double-blind study, they conclude that intraperitoneal infiltration with local anaesthetics significantly reduces pain intensity scores in the early postoperative period and helps in improving the postoperative recovery profile and outcome. In this study, ropivacaine (0.375%) proved more efficacious and longer acting with a higher intensity of postoperative analgesia than bupivacaine (0.25%) (744).

Chen and colleagues claim that elevated NLR (≥ 2.49) is a promising independent predictor of poor survival after hepatectomy in patients with intrahepatic cholangiocarcinoma. In this retrospective study, elevated NLR proved significantly associated with recurrence-free survival and overall survival (745).

Min and co-workers corroborate the prognostic value of pretreatment NLR in patients with liver cancer. In their meta-analysis, elevated NLR was associated with worse overall survival, recurrence-free survival, and disease-free survival (746).

Dumitrascu et al. conclude that NLR is a novel independent predictor for severe morbidity after major hepatectomies for perihilar cholangiocarcinoma. In their study, a NLR > 3.3 proved a significant and independent prognostic factor for severe complications following hepatectomy (747).

Haruki and Lee also confirm the prognostic value of pretreatment NLR. Preoperative NLR (≥ 3.0) was a significant indicator of long-term outcome in patients with carcinoma of the ampulla of Vater after pancreaticoduodenectomy (748), whilst pretreatment NLR (> 5.0) was predictive of survival in patients with advanced cholangiocarcinoma undergoing chemotherapy (749).

Cho and colleagues have retrospectively investigated the clinical significance of systemic inflammation in patients with advanced biliary tract cancer. Additionally, they also co-analyzed the dynamics of NLR and PLR during chemotherapy. Results show that patients with a high NLR (> 3.8) and PLR (> 121) had significantly worse overall survival. High NLR with increased NLR after chemotherapy was also associated with worse overall survival and progression-free survival. Results were similar for PLR. Therefore, the authors

conclude that systemic inflammation predicts overall survival in patients with advanced biliary tract cancer who are receiving palliative chemotherapy. In addition, dynamic change of NLR/PLR during chemotherapy might also help to predict a more accurate prognosis (750).

Sagib et al. have performed a systematic review in which the prognostic significance of preoperative inflammatory markers in resected gallbladder cancer was investigated. Based on their results, they conclude that elevated preoperative inflammatory markers (NLR, CRP and Glasgow Prognostic Score) are inversely related to survival outcomes (751).

Based on the results of their meta-analysis, Zhou and Luo state that elevated pretreatment platelet-to-lymphocyte ratio (PLR) may be an unfavourable prognostic factor for clinical outcomes in patients with biliary tract cancer, since elevated PLR was significantly associated with decreased overall survival and recurrence-free survival (752).

Mao and co-workers have explored the relationship between clinicopathological features and the distribution of neutrophils in the tumour microenvironment in cholangiocarcinoma. The results show that a high density of neutrophils in tumour tissue, as reflected by a positive expression level of CD15, was significantly associated with shorter overall survival. In other words, a more pronounced inflammatory status with a higher density of neutrophils in tumour tissue proved to be an independent risk factor for overall survival (753).

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 (754).
Musri’s group also reports that increased NLR (> 3.34) is an independent prognostic factor associated with shorter survival in patients with metastatic gastric cancer (755).

Kim and colleagues confirm that preoperative NLR and old age are significant, independent prognostic factors for overall survival in patients with gastric cancer. In their retrospective study, a high NLR (≥ 1.7) was significantly associated with worse overall survival in patients undergoing surgery for this type of cancer (756).

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) (757).
Tanaka and Dogan confirm these findings. The used cut-off point for the NLR in both retrospective studies was 2.5 (758,759).

Ock and colleagues also report that NLR is a significant poor prognostic factor in advanced gastric cancer. Furthermore, NLR appears to be mainly associated with osteopontin and interleukin-6 (760).

Li and co-workers claim that adjuvant immunotherapy with autologous cytokine-induced killer cells (CIK) prolongs disease-free survival in postoperative patients with gastric cancer and that preoperative NLR is an independent prognostic factor for disease-free survival. Low NLR (< 2.995) predicted significant benefits from the CIK immunotherapy, while high NLR foreboded the requirement of more cycles of CIK treatment or other stronger immunotherapy to improve the survival rate of patients (761).

With respect to recurrent gastric cancer, Migita and colleagues state that inflammation-based markers, including the NLR and prognostic nutritional index (PNI), are simple and useful clinical biomarkers that can be used to predict survival (762).

On the contrary, Min's group reports that postoperative NLR change (NLRc) reflects the dynamic change of balance between host inflammatory response and immune response after treatment. Since NLRc was significantly associated with patient survival and the initial pretreatment NLR (iNLR) was not, the authors conclude that NLRc could be a better indicator than iNLR for predicting survival in gastric cancer patients (763).

Aldemir et al. report that NLR and PLR have a prognostic value in patients with advanced gastric cancer who received chemotherapy. However, in patients with local gastric cancer undergoing surgery and receiving chemotherapy, only high platelet count was associated with better overall survival. Both NLR and PLR had no effect on prognosis in this group of patients (764).

Wang‘s group states that baseline NLR and PLR, as well as changes of NLR and PLR following chemotherapy can predict the prognostic results in patients with unresectable gastric cancer (765).

Chen and colleagues have conducted a meta-analysis to determine the predictable value of NLR in the clinical outcome of gastric cancer patients. Their analysis indicated that elevated pre-treatment NLR predicted poorer overall survival and progression-free survival. Furthermore, over a 3-year follow-up period, high NLR was a significant predictor of poor outcomes at year 1, year 2, and year 3 (766).

Kim et al. have compared NLR and PLR as prognostic factors in gastric cancer and report that NLR, in contrast to PLR, is an independent prognostic factor for overall survival in gastric cancer patients undergoing curative surgery (767).

Deng and colleagues support the prognostic value of NLR in gastric cancer patients undergoing gastrectomy. In their retrospective study, NLR proved to be an independent prognostic indicator for both cancer-specific survival and disease-free survival (768).

Gunaldi et al. also support the predictive properties of NLR and PLR in patients with various stages of gastric cancer. In their multicenter study NLR correlated significantly with status of lymph node metastasis and the stage of the disease. PLR correlated with the depth of tumour invasion and stage of gastric cancer (769).

Sun and co-workers have investigated whether the combination of preoperative albumin concentration (COA) and NLR can predict overall survival better than other prognostic indices in patients after curative resection for gastric cancer. In this retrospective study,

COA-NLR score was determined by giving patients a COA-NLR score of 2 when the albumin concentration was above 35 g/L and the NLR 2.3 or higher. Patients with one of these conditions were allocated a score of 1. Patients with neither of these conditions received a COA-NLR score of 0. Results showed that COA-NLR score was independently associated with overall survival. Moreover, this association was significantly higher than that of the NLR alone, the Glasgow prognostic score, and the PLR. The authors therefore conclude that the preoperative COA-NLR index is useful for predicting postoperative overall survival in patients with gastric cancer and can be used to guide targeted therapy (770).

Mohri's group even reports that elevated NLR could trigger postoperative infectious complications and increase the risk or recurrence in patients with postoperative infectious complications after gastrectomy. In their retrospective study, preoperative NLR independently predicted the development of postoperative infectious complications, but not the development of postoperative non-infectious complications after gastrectomy. Both elevated NLR and postoperative infectious complications were independently associated with worse long-term survival. Patients with both elevated NLR and the development of postoperative infectious complications had the worst long-term survival. In other words, NLR independently predicted the development of postoperative infectious complications and lower survival after gastrectomy (771).

Jiang et al. have retrospectively investigated the pretreatment NLR in patients with gastric cancer and compared this with the NLR in patients with gastric polyp or gastric stromal tumour. Results revealed a significantly higher NLR in the gastric cancer cohort. NLR was also an independent predictor of gastric cancer. In addition, NLR was positively correlated with tumour size, distant metastasis, and overall stage (772).

Based on the results of their prospective study, Lou cum suis report that preoperative PLR and NLR correlate with early gastric cancer lymph node metastasis. The optimal cut-off values were 106 and 2.97, respectively (773).

Arigami and co-workers state that the combination of fibrinogen concentration and NLR may be a potentially useful blood marker for predicting tumour progression and the prognosis of patients with gastric cancer (774).

Pan and colleagues confirm that NLR is an independent predictor of gastric cancer survival. However, they claim that the Glasgow prognostic score (GPS) and TNM stage are more robust predictors of gastric cancer survival as compared to NLR and PLR (775).

Finally, Sun et al. have performed a systematic review and meta-analysis in which the predictive value of NLR on gastric cancer treatment oucomes was investigated. Their results show that elevated pretreatment NLR is associated with poor outcome in patients with gastric cancer. Therefore, the authors conclude that the ability to use NLR to evaluate the status of patients may be used in the future for personalized cancer care (776).

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 (777). Benevides et al. report similar results in the case of invasive breast cancer (450).

Lian et al. support the predictive role of NLR and PLR in the early diagnosis and prognosis in patients with resectable gastric cancer. In their study, preoperative NLR and PLR were significantly higher in gastric cancer patients compared to healthy subjects. Low preoperative NLR and PLR (< 4.02, respectively < 208) correlated with better clinicopathological features, including decreased depth of invasion, less lymph node metastasis and early tumour stage. Higher preoperative NLR and PLR were associated with decreased overall survival and disease-free survival (778).

Chen and colleagues point out that pretreatment baseline neutrophil count and chemotherapy-induced neutropenia may be conveniently available as prognostic biomarkers in advanced gastric cancer. This conclusion is based on the results of their retrospective

study in which mild chemotherapy-induced myelosuppression was associated with better overall survival, whereas a high baseline neutrophil count (> 7.5 x 10^9/L) was associated with a worse prognosis (779).

Atila et al. state that NLR can provide information about inflammatory status, tumour aggressiveness and prognosis in patients with gastrointestinal stromal tumours (GIST) (780).
Kargin et al. even claim that preoperative NLR can be used as an indicator of high-risk tumours and poor prognosis in patients with gastrointestinal stromal tumors (781).

Jiang and co-workers support this claim. In their retrospective study, a high NLR (≥ 2.7) was significantly associated with shorter overall survival in patients undergoing curative resection of GIST with or without adjuvant/palliative imatinib treatment. Furthermore, increased NLR indicated poor overall survival in patients regardless of receiving imatinib treatment or not. The authors therefore conclude that elevated NLR can be seen as an independent adverse prognostic factor. Elevated NLR predicts poor clinical outcome in GIST patients and may serve as a cost-effective and broadly available independent prognostic biomarker (782).
Stotz et al. support these findings. In their analysis, low Hb, elevated white blood cell count, elevated dNLR, and elevated PLR were independent prognostic factors for a worse clinical outcome in GIST patients after curative resection (783).

Xiao and colleagues state 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 (784). Unfortunately, the cut-off value for defining high NLR in the identified studies had not been unified.
Gomez et al. support the predictive properties of preoperative NLR after curative resections for hepatocellular carcinoma (785).

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 (786).

Okamura and colleagues also confirm that preoperative NLR is an important prognostic factor for TNM stage I hepatocellular carcinoma after liver resection with curative intent. The best cut-off value for NLR in this retrospective study was 2.8. They conclude that these results suggest that the NLR may reflect the malignant potential of hepatocellular carcinoma (787).

Yang's group claims that both NLR and lymphocyte-to-monocyte ratio (LMR) are independent prognostic factors for disease-free survival in hepatocellular cancer patients undergoing hepatectomy (788).

Lin et al report that elevated NLR is an independent predictor for poor overall and recurrence-free survival in patients with intrahepatic cholangiocarcinoma. Furthermore, elevated NLR appears to be associated with poor anti-tumour immunity (lymphocytes, T cells and CD8+ cells) (789).

Heindryckx and Gerwins expand further on the role of inflammation in the development and growth of hepatocellular carcinoma. In their paper, the authors focus especially on the stromal environment, consisting of several cell types, including hepatic stellate cells, macrophages and endothelial cells. These cells are believed to play an important and active role in tumour initiation, progression and metastasis. Furthermore, these cells are influenced by the tumour itself to create an environment that is beneficial for sustaining tumour growth. According to the authors, hepatic stellate cells play a key role in tumour initiation. Once liver damage has occurred, stellate cells are activated and these activated stellate cells increase the production of angiogenic factors and stimulate the recruitment of macrophages.

This increase of angiogenic factors (which are secreted by activated stellate cells, macrophages and tumour cells) induces the formation of new blood vessels, thereby supplying the tumour cells with more nutrients and oxygen, and consequently supports tumour growth. In addition, tumour associated macrophages are recruited by the secretion of chemokines by the tumour cells. On their turn, these tumour associated macrophages infiltrate the tumour environment and exert a tumour promoting effect by secreting growth factors, stimulating angiogenesis and influencing the activation of hepatic stellate cells (790).

Neofytou 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 and overall survival in univariate analysis, only PLR remained significant in multivariate analysis. A NLR > 2,4 and a PLR > 150 were considered to be elevated (791).

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 (161). Ahmad, based on a systematic review, states that NLR may be useful as a predictor in patients with pancreatic ductal adenocarcinoma (792).

Arima and co-workers claim that preoperative NLR is a useful supportive marker to predict intraductal papillary mucinous cancer (IPMC). In their retrospective study preoperative NLR was significantly higher in patients with IPMC than in patients with intraductal papillary mucinous adenoma and healthy volunteers. Furthermore, NLR was significantly reduced after curative tumour resection. The main duct type and NLR > 2.074 were independent predictors of IPMC in all patients (793).

Goh and colleagues report that PLR (platelet-to-lymphocyte ratio) is a useful tool for predicting malignancy in surgically treated mucin-producing pancreatic cystic cancers (794).

Arima et al. state that high NLR (> 5.0) could independently predict the occurrence of pancreatic ductal adenocarcinomas in pancreatic neoplastic disease irrespective of other tumour markers in pancreatic disease (795).

Qi and co-workers share the view that systemic inflammatory response (SIR) markers, including the NLR, can be used to determine optimal therapeutic strategies for individual patients and to predict pancreatic cancer prognosis (796).
Asari et al. support the predictive properties of preoperative NLR (and PLR) in patients with borderline resectable pancreatic ductal adenocarcinoma (797).
Gemenetzis and co-workers report that NLR is an independent predictive marker for the presence of intraductal papillary mucinous neoplasms-associated invasive carcinoma of the pancreas (798).

Lee's group also concludes that systemic inflammation-based markers, including increases in the NLR and CRP/albumin ratio, may be useful for predicting pancreatic cancer prognoses (799).

Alagappan et al. report that preradiotherapy NLR > 5.0 and low albumin levels correlate with decreased survival in patients with locally advanced pancreatic adenocarcinoma treated with stereotactic body radiotherapy (800).

By contrast, Chawla and co-workers were unable to detect any relationship between pretreatment NLR and PLR and survival in patients who underwent pancreatectomy for pancreatic ductal adenocarcinoma (801).

Li and colleagues confirm these findings. 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 (802).

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 (803).

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 (804).

Sukato and co-workers confirm the prognostic role of NLR in patients with unresectable hepatocellular carcinoma treated with radioembolization. Based on the results of their retrospective study, the authors conclude that elevated NLR (NLR ≥ 5.0) is an independent predictor of worse survival (805).

D'Emic and co-workers also confirm that both pre- and/or post-treatment NLR and/or PLR are predictive of clinical outcome in patients undergoing selective internal radiation. Furthermore, they report that the largest increase in risk of death as well as local and extrahepatic disease progression was related to change in PLR (806).

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 (807).

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 (808).

Ben et al. also state that pre-treatment 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) (809).

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 (810).

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 (811).

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 (812).

Ishizuka et al. confirm the prognostic value of the NLR as well, albeit in combination with the platelet count. Based on their study results, the authors state that the preoperative combined platelet count and neutrophil-to-lymphocyte ratio is a useful predictor of postoperative survival in patients undergoing surgery for gastric cancer (813).
Li et al. also claim that NLR is an independent predictor of survival in gastric cardia adenocarcinoma (814).

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 (815). 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 (816).

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 (817).
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 (818).

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 (819).

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 (820).

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 (821).

Finally, Gao et al. report to have investigated the prognostic value of pre-treatment NLR in patients with hepatocellular carcinoma and compared it with the Child-Pugh class and Model for End-Stage Liver Disease (MELD) score. Their results showed that the prognostic value of pre-treatment NLR (≥ 2.7) is superior to that of MELD stage or Child-Pugh class, and that it correlates with that of Barcelona-Clinic Liver Cancer (BCLC) and Tumour, Node, Metastasis (TNM) staging scores (822).

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

Nevertheless, Jaramillo-Reta and colleagues report that NLR acts as a predictor of surgical mortality and survival in complex surgery of the upper gastroinstestinal tract. In their retrospective study, a high NLR (> 4.5) was significantly associated with reduced survival in patients with malignant neoplasms of the upper gastrointestinal tract (823).

Khan's group has retrospectively investigated which prognostic factors are associated with survival in advanced appendiceal cancers. Results showed that only histopathologic subtype and gender were associated with overall survival. Baseline platelet levels, NLR, and PLR were not predictive of survival in this group of patients (824).

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 (821), this beneficial effect was not encountered in patients undergoing resection of the colon (825).

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 (110-114).
Nan and colleagues claim that regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with lower risk of colorectal cancer. This claim is based on the results of a case-control study using data from 5 case-control and 5 cohort studies including colorectal cancer patients (n= 8634) and matched controls (n= 8553). However, this association was reported to differ according to genetic variations at 2 single-nucleotide polymorphisms at chromosomes 12 and 15. Regular use was associated with a lower risk of colorectal cancer among individuals with rs16973225-AA genotype, but was not associated with risk of colorectal cancer among those with the less common (9%) AC or CC genotypes (826).

Wakeman et al. confirm that er is increasing evidence that continuing use of low-dose aspirin reduces long-term incidence of colorectal cancers. Albeit, they conclude that there is not enough evidence to support the implementation of a chemopreventative agent for general use at this point in time (827).

By contrast, Cao and co-workers claim that regular use of aspirin is associated with a lower risk of colorectal carcinomas with low concentrations of tumour-infiltrating lymphocytes (TILs). Therefore, the authors conclude that the immune response in the tumour microenvironment could be involved in the chemopreventive effects of aspirin (828).

As mentioned previously, Vaughan et al. report that aspirin use may prevent colon, breast, pancreatic, and ovarian cancer in elderly women (414).

Based on the results of their multi-ethnic cohort study, Park and colleagues conclude that the benefit of NSAIDs for colorectal cancer may be strongest for white men and generalizes to African American, Japanese and Latino but not to native Hawaiian men (829). A good explanation for these findings can't readily be given.

Veettil et al. have performed a systematic review with meta-analysis and trial sequential analysis of randomized clinical trials in which the effects of aspirin and non-aspirin non-steroidal anti-inflammatory drugs on the incidence of recurrent colorectal adenomas was investigated. Based on the results, the authors conclude that their findings confirm the beneficial effect of low-dose aspirin on the recurrence of any adenomas. However, the effect on advanced adenomas was inconclusive. COX-2 inhibitors appear to be more effective in preventing recurrence of adenomas (830).

In turn and based on the results of their cross-sectional study, Shaw and colleagues claim that dietary fibre intake and NSAID use are associated with a decreased risk of having high-risk adenomatous polyps at screening. These were defined as adenomas with villous histology, high-grade dysplasia, size ≥ 10 mm or ≥ 3 polyps (831).

Rigas and Tsioulias expand further on the chemopreventive action of NSAIDs (832).

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 (833).

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 (834).

Sun and co-workers have performed a meta-analysis in which the impact of anaesthetic techniques on survival for patients with colorectal cancer was studied. Based on the results they conclude that general anaesthesia combined with epidural analgesia is associated with significantly longer overall survival, but not with prologend recurrence free survival (835).

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 (138). 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 (836).

By contrast, Myles found no association with recurrence free survival when perioperative neuraxial blockades were administered during oncological laparotomies (837).
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 (838).

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 (839).

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 resection 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 (840).

Taupyk et al. report similar findings with respect to fast-track laparoscopic surgery. In their blinded randomized trial, patients with colorectal cancer underwent laparoscopic colorectal resection. One group underwent conventional laparoscopic surgery, the other group underwent fast-track laparoscopic surgery: no preoperative mechanical bowel preparation, epidural analgesia, early restoration of diet and early postoperative ambulation. Outcome measures, length of hospital stay, postoperative surgical stress response (CRP) and postoperative complications were compared between the two groups. Patients in the fast-track surgery group had shorter hospital stay and quicker recovery of bowel function without difference in postoperative complications (841).

Based on the results of their cohort study, Senagore and co-workers conclude that thoracic epidural analgesia (TEA) shortens the length of stay after laparoscopic segmental colectomy, and that TEA has a significant and favourable impact on dietary tolerance and therefore appears to be an important component of the postoperative care protocol (842).

Subsequently, the same group of investigators has performed a prospective randomized trial in which the use of thoracic epidural analgesia was compared with morphine patient-controlled analgesia (PCA) in patients undergoing laparoscopic colectomy. The results of this prospective trial indicate that TEA significantly improves early analgesia but does not affect the length of hospital stay. Apparently, the use of TEA did not result in earlier

dismission from hospital as reported previously. On the other hand, its use did not result in prolonged hospital admission either (843).

Zgaia's group claims that patient-controlled epidural analgesia (PCEA) provides better postoperative pain control, and improves postoperative recovery after gastrointestinal cancer surgery compared with conventional morhine treatment. Therefore, PCEA is more acceptable than conventional pain management for this type of surgery. This claim is based on the results of their prospective, randomized and single centre study (844).

Liu et al. have performed a meta-analysis in which the effects of thoracic epidural analgesia on clinical outcomes of laparoscopic colorectal surgery were compared with patient controlled analgesia (PCA). Their results show that TEA is associated with better postoperative pain alleviation and lower risk of nausea and vomiting. These benefits were not at the expense of increased risks of any major complications, or longer hospital stay (845).

Based on the results of their randomized controlled trial, Barr and co-workers conclude that thoracic epidural analgesia significantly, albeit transiently, attenuates the stress response following laparoscopic colorectal surgery within an enhanced recovery after surgery protocol. In this trial, patients received either thoracic epidural analgesia or continuous local anaesthetic infusion to the extraction site via wound infusion catheter (846).

Song's group reports similar findings. In their prospective and randomized study, general anaesthesia combined with epidural analgesia produced milder deleterious effects on the immune function of perioperative critically ill patients than general anaesthesia combined with intravenous analgesia (847).

Based on their meta-analysis, Gendall and colleagues conclude that randomized controlled trials have shown a benefit for epidural analgesia on pain relief, and ileus, and possibly respiratory complications without affecting hospital length of stay in patients undergoing colorectal surgery (848).

Warschkow and Fotiadis confirm the benefits of thoracic epidural analgesia in open colorectal cancer surgery. Warschkow et al. report that the application of TEA leads to a reduction in pulmonary complications without effects on anastomotic leakage risk and/or surgical site infections (849).
Fotiadis and Shi report that TEA enhances recovery after gastroinstestinal surgery (850,851).
It has to be mentioned that these studies failed to demonstrate any beneficial effect of epidural analgesia on anastomotic leakage risk.

An and colleagues have conducted a systematic review and meta-analysis of anaesthesia methods on postoperative major adverse cardiac events and mortality after non-cardiac surgeries. Based on the results, they claim that sevoflurane anaesthesia, or epidural analgesia combined with general anaesthesia provides short-term myocardial protective effects in high-risk cardiac patients undergoing intermediate- or high-risk non-cardiac surgeries (852).

Nonetheless, Eto's group claims that TEA may not be necessary for enhanced recovery after surgery (ERAS) in laparoscopic colorectal surgery. This claim is based on the results of their retrospective study, in which thoracic epidural analgesia was compared with multimodal analgesia. In this study, factors that demonstrated significant correlation with hospital stay did not include analgesia (853).
Hanna et al. second this claim. In their randomized, single centre study, epidural analgesia revealed no added clinical benefit in patients undergoing minimally invasive colorectal surgery. Moreover, there was a trend toward higher total narcotics use and complications with epidural analgesia, such as hypotensive periods (854).

Nonetheless, Onoglu and co-workers report that thoracic epidural analgesia has the ability to reduce mesenteric ischaemic-reperfusion injury (855).

Bardia et al. even claim that combined epidural analgesia and general anaesthesia is associated with improved survival and significantly lower risk for mortality and morbidity in patients undergoing open elective abdominal aortic aneurysm repair (856).

Interestingly, Demaree and colleagues report that an epidural blood patch bears low risk of seeding cancer cells to the central nervous system when used to treat postdural puncture headache that is unresponsive to conservative treatment (857).

Roeb's group concludes that with respect to pain intensity, satisfaction, and relatable side-effects, epidural analgesia appears to be superior compared to systemic analgesia after abdominal surgeries. For this analysis, collected data from more than 30.000 patients on pain on the first postoperative day in hospitals worldwide were used (858).

Guay et al. have performed a meta-analysis in which the effects of postoperative epidural analgesia with local anaesthestics were compared with postoperative systemic or epidural opioids in terms of return of gastrointestinal transit, postoperative pain control, postoperative vomiting, incidence of anastomotic leak, length of hospital stay and costs after abdominal surgery. There results showed that an epidural containing a local anaesthetic is significantly associated with a decreased time to first flatus (high quality of evidence). This effect was proportionate to the concentration of local anaesthetic used. Furthermore, pain on movement at 24 hours after surgery was also reduced (moderate quality of evidence). Finally, epidural analgesia was associated with a reduced length of hospital stay for open surgery (low quality of evidence). There were no differences in the incidence of vomiting or anastomotic leak (low quality of evidence) (859).

As mentioned previously, Kuo et al. have prospectively compared the effects of thoracic epidural analgesia and intravenous infusion of lidocaine on pain and bowel function in patients undergoing colonic surgery. Patients were randomly allocated to one of the following 3 groups. The TEA group received lidocaine epidurally and saline intravenously. The IV group received the same amount of lidocaine intravenously and normal saline epidurally. The control group received normal saline via both routes. Based on the results, the authors report that thoracic epidural analgesia results in better pain relief, lower opioid consumption, earlier return of bowel function, and lesser production of cytokines than intravenous lidocaine during 72 hours after colonic surgery. The IV group scored better than the control group (661).

Interestingly, based on the results of their prospective, randomized double-blinded investigation, Hodgson and Liu report that epidural analgesia is able to reduce volatile anaesthetic requirement by 34%. Furthermore, this reduction in volatile anaesthetic requirement is not a result of systemic lidocaine absorption from the epidural space since plasma lidocaine concentrations in the epidural and intravenous group were similar (860).

Vogelaar and colleagues present a review of literature in which the association of the use of epidural analgesia and survival in colon cancer surgery is addressed (861).

With respect to the insertion of the epidural catheter, Hasanin et al. report that preprocedural ultrasound imaging increases the incidence of first pass success and reduces the catheter insertion time compared to the manual palpation method (862).

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 (863).

Other studies have confirmed that local anaesthetics exhibit anti-tumour effects (53-61). Piegeler demonstrated that only local anaesthetics of the amide type display these inhibiting properties, in contrast to local anaesthetics of the ester type (57).
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 (58).
Lucchinetti, on the other hand, reports that lidocaine, ropivacaine, and bupivacaine reduce proliferation of mesenchymal stem cells (59).

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 (864).

However, Owusu-Agyemang and colleagues demonstrate that the combined use of preoperative celecoxib, tramadol and pregabalin followed by intraoperative TIVA infusions of propofol, dexmedetomidine, ketamine and lidocaine is not associated with a reduction in length of hospital stay or complications by organ system (865).

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 (866).

Tylman and co-workers, in their turn, report that IL-17 serum levels are higher in colorectal cancer patients anaesthetized with sevoflurane and fentanyl compared with patients anaesthetized with propofol and fentanyl. Otherwise, both anaesthetic techniques induced similar inflammatory responses (867).

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) (868).

Piccioni et al. conclude that epidural analgesia ensures adequate pain relief and is well tolerated by patients after cytoreductive surgery with peritonectomy combined with heated intraperitoneal chemotherapy (869).

These findings are confirmed 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 (870). However, volume of blood transfused, intraoperative vasopressors use, time to extubation, and length of hospital stay was not affected.

Kajdi and colleagues also support the use of thoracic epidural analgesia (TEA) in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. In their retrospective analysis, the use of TEA had a significant opioid-sparing effect, albeit without reduction of postoperative ventilation and ICU stay, nor shortened time to first bowel passage. However, the type and amount of resuscitation fluids used, as well as blood transfusions, were associated with patients' outcome. Hydroxyethyl starch (HES) administration had a significant negative impact on renal function, especially in younger patients. The need for blood transfusion was also clearly associated with an increased risk for major complications (871).

Korakianitis et al. support the belief that epidural analgesia is a safe option in cytoreductive surgery and HIPEC despite certain intraoperative fluctuations in coagulation parameters (872).

Holler and co-workers claim that epidural analgesia is positively associated with improved long-term survival in patients who undergo surgery for colorectal cancer without metastases. This claim is based on the results of their meta-analysis (873).

Chen and Miao also have conducted 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) (874).

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 analogue 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 (875).

Vogelaar et al. claim that epidural analgesia is associated with better survival in colon cancer. This claim is based on the results of their retrospective study in which 588 primary colon cancer patients were investigated. Five-year survival was significantly higher in patients receiving epidural analgesia compared to those who did not (876).

Weng and co-workers have performed a meta-analysis (21 studies involving over 51500 patients) in which the effects of neuraxial (epidural and spinal) anaesthesia on cancer recurrence and survival after cancer surgery were investigated. Their results show that neuraxial anaesthesia may be associated with improved overall survival and recurrence-free survival in patients undergoing cancer surgery. Especially in case of colorectal cancer, there was a strong positive association between neuraxial anaesthesia and improved overall survival (877).

Xu and colleagues have evaluated the effects of serum from patients undergoing colon cancer surgery receiving propofol anaesthesia and thoracic epidural analgesia on colon cancer cell biology. Based on the results of this prospective, randomized study, they report that serum from patients receiving propofol anaesthesia with thoracic epidural analgesia inhibited proliferation and invasion of LoVo colon cancer cells, and induced more apoptosis than that of patients receiving sevoflurane anaesthesia with opioid analgesia in vitro. So the authors conclude that anaesthetic technique might influence the serum milieu in a way that affects cancer cell biology and, therby, tumour metastasis (878).

Wu and co-workers report that the development and implementation of an enhanced recovery pathway program (ERP) in colorectal surgery patients has resulted in a 45% reduction in length of hospital stay. The reported goals of the perioperative anaesthesiology pathway were: achieving superior analgesia, minimizing postoperative nausea and vomiting, facilitating patient recovery, and preserving perioperative immune function (partly by minimizing perioperative opioid use. Furthermore, patient satisfaction scores improved from the 37th percentile pre-implementation to > 97th post-implementation (879).

Fujita and colleagues have addressed the short-term surgical stress response following colectomy by measuring reactive oxygen and free radicals. They report that reactive oxygen metabolites (ROM) declined immediately following surgery compared to immediately prior to surgery, and a tendency was observed for these values to increase again one day following surgery. However, no significant change was observed in the surgical stress level between patients following laparoscopy and laparotomy. The low-invasiveness of laparoscopic surgery was not indicated in the ROM value one day following surgery, most probably because pain control offset the level of surgical stress. Indeed, pain scores one day after surgery were significantly lower in the epidural anaesthesia group compared to the opioid intravenous injection group (880).
In other words, the beneficiary effects of laparoscopic surgery compared to laparotomy, with subsequent lower levels of surgical stress response, were neutralized by less effective pain control in the intravenous opioid group compared to the epidural anaesthesia group. It remains to be seen whether the attenuation of the surgical stress response is a result of more adequate pain control brought about by epidural analgesia, or the direct result of the effects of epidural analgesia on the stress response itself.

Day et al. have conducted a prospective and randomized trial in which the stress response from two different methods of analgesia after laparoscopic colorectal surgery was investigated. Patients were randomly allocated to either spinal analgesia or morphine patient-controlled analgesia (PCA). Spinal analgesia was administered by injecting 2.5 ml of a 0.5 % hyperbaric bupivacaine with 0.25 mg diamorphine. PCA consisted of administering 10 mg morphine towards the end of surgery and connecting a pump to deliver morphine on demand at a dose of 1 mg, with a 5-minute lock-out and a maximum dose of 20 mg every 4 hours. Results revealed that at 3 hours after surgery cortisol and glucose levels were significantly lower in the spinal analgesia group than in the PCA group. At six hours after surgery cortisol and glucose levels were statistically comparable in both groups. This reflects the expected duration of the effect of spinal analgesia. The postoperative inflammatory response was not attenuated in the spinal analgesia group compared with that in the PCA group. However, the global inflammatory response was reduced in magnitude and time in comparison with data available from patients undergoing open colorectal

resection. Overall parenteral morphine use was significantly reduced in the spinal analgesia group (881).

Whelan and co-workers claim that postoperative cell-mediated immune function is better preserved in patients after laparoscopic-assisted colorectal resection than after open resection. This claim is based on the measurement of serial delayed-type hypersensitivity (DTH) responses (882).
Other studies confirm that immune function remains highest in patients undergoing laparoscopic colorectal surgery within a fast track program (883,884). It has to be mentioned that thoracic epidural analgesia was included within the fast track program.

Based on the results of their prospective, randomized trial, Mari's group reports that Enhanced Recovery After Surgery (ERAS) program reduces IL-6 secretion and postoperative CRP levels in colorectal laparoscopisc surgery, hereby attenuating the surgical stress reponse (885).

Siekmann and colleagues claim that open surgery, compared to laparoscopic surgery, has a greater impact on the inflammatory mediators than epidural analgesia versus intravenous analgesia. In their prospective, randomized study, patients undergoing laparotomy had significantly higher levels of IL-6, IL-8, and IL-10 compared to patients undergoing laparoscopic surgery. There were no significant differences in inflammatory mediators between patients receiving epidural analgesia and intravenous analgesia. Therefore, the authors conclude that surgical, but not analgesic technique affects postoperative inflammatory response following colorectal surgery (886).

With respect to the surgical stress response, Krog's group demonstrates that patients undergoing laparoscopic aortobifemoral bypass surgery achieve earlier hormonal homeostasis after surgery compared to patients undergoing open aortabifemoral bypass surgery. However, laparoscopic surgery patients had higher levels of ACTH, aldosterone and cortisol during surgery (887).

Behrenbruch and colleagues expand further on the relation between surgical stress response and promotion of metastasis in colorectal cancer (888).

Schietroma et al. have prospectively investigated the effects of surgery (laparotomy versus laparoscopic resection for colon cancer) on gut barrier function and systemic endotoxemia. Their results indicate that both laparoscopy and laparotomy result in an increase in intestinal permeability and systemic endotoxemia, without statistically significant difference between both types of surgery (889).
Zaborin and co-workers demonstrate that surgical stress, antibiotic exposure, and tissue injury results in caecal crypt evacuation of its microbiotica. In addition, crypts devoid of their microbiota display loss of regenerative capacity. Faecal microbiota transplantation restores the caecal crypts' microbiota, normalizes homeostasis within crypts, and re-establishes crypt regenerative capacity (890).

Ekeloef's group shows that the reactive hyperaemia index is attenuated in the first days after colon cancer surgery indicating acute endothelial dysfunction. According to the authors this finding provides a rationale for investigating the hypothesized association between acute endothelial dysfunction and cardiovascular complications after non-cardiac surgery (891).

Interestingly, Jeon et al. claim that intravenous high dose vitamin C (50 mg/kg) decreases postoperative pain during the first 24 hours and reduces opioid consumption in the early postoperative period in patients undergoing laparoscopic colectomy. This claim is based on the results of their randomized controlled study (892).

Halabi and colleagues have performed a retrospective nationwide analysis of the use of epidural analgesia and its outcomes in laparoscopic colorectal surgery. Their results show that the perioperative use of epidural analgesia in laparoscopic colorectal surgery is very limited in the United States. Its estimated use was 2.14%. Epidurals were more likely to be used in larger teaching hospitals, cancer surgery, and rectal operations. On case-matched analysis, epidural analgesia was associated with a longer hospital stay by 0.60 day, higher hospital charges by $ 3733,- and higher rate of urinary tract infection. Epidural analgesia did

not affect the incidence of respiratory failure, pneumonia, analstomotic leak, ileus, or urinary retention (893).

Waterland et al. have investigated the prognostic value of CRP to predict anastomotic leakage after open and laparoscopic surgery. They demonstrate that CRP levels are higher after open colorectal surgery compared with laparoscopic surgery, both with and without anastomotic leakage. Anastomotic leakage generated a significant detectable increase in CRP within 2-4 days after surgery (894).

Facy and colleagues have conducted a prospective, observational study in which the effects of surgical approach on inflammatory markers were investigated. 501 patients undergoing laparoscopic and/or open colorectal surgery were included. The incidence of intra-abdominal infections was 11.8%. The median levels of CRP and procalcitonin (PCT) were lower in the laparoscopy group at each postoperative day compared with the laparotomy group. In patients without intra-abdominal infections, these markers were also lower in the laparoscopy group but were not different in patients presenting with intra-abdominal infections. In the laparoscopy group, CRP at postoperative day 4 (cut-off of 100 mg/L) was the most accurate predictor of overall and intra-abdominal infections. Based on these results, the authors conclude that the impact of infection on inflammatory markers is more important than that of the surgical approach. Defining a specific cut-off value for early discharge according to the surgical approach is not justified. A patient with CRP values lower than 100 mg/L on postoperative day 4 can be safely discharged (895).

Juvany’s group demonstrates that the combination of immediate postoperative lactate and CRP at 48 hours prove to be useful in predicting organ-space surgical site infection after elective colorectal operations. Consequently, the authors stress the importance op peri-operative lactate assessment (896).

Labgaa et al., on the other hand, conclude that early postoperative decrease of serum albumin correlates with the extent of surgery, its metabolic response, and with adverse outcomes such as complications and length of hospital stay. In this prospective cohort study, a decreased concentration of serum albumin ≥ 10 g/L on postoperative day 1 was associated

with a threefold increased risk of overall postoperative complications and may thus be used to identify patients at risk (897).

However, it has to be mentioned that laparoscopic surgery using carbon dioxide pneumoperitoneum has been shown to increase the surgical stress response by itself. By contrast, intraoperative thoracic epidural anaesthesia was shown to attenuate the stress response (898-904,1366).

Shoar et al. have performed a prospective, double-blinded, randomized controlled trial in which the systemic stress response in patients undergoing laparoscopic surgery was investigated. Patients were randomized to either low-pressure or standard-pressure CO2 pneumoperitoneum laparoscopic cholecystectomy. Results showed that patients undergoing laparoscopic surgery with low-pressure pneumoperitoneum experienced the same systemic stress response compared to patients undergoing laparoscopy with standard-pressure pneumoperitoneum. Furthermore, there were no differences in intraoperative intravenous volume administration, urine output and/or operative time (905). Apparently, even low-pressure CO2 pneumoperitoneum results in a significant stress response, which in turn may affect patient's own immunity and defence mechanisms. Although postoperative cell-mediated immune function is better preserved in patients after laparoscopic-assisted surgery than after open surgery, the inflation of the abdomen alone results in a significant stress response. In our opinion, one should take the effects of pneumoperitoneum during laparoscopic surgery into account when deciding which anaesthetic technique should be used with resepct to the attenuation of the surgical stress response.

Strikingly, Borges and co-workers demonstrate that patients undergoing conventional laparoscopic cholecystectomy exhibit less surgical stress (lower expression of IL-17) compared with patients undergoing single-port laparoscopic cholecystectomy (906). Apparently, single-port laparoscopic surgery leads to more extensive tissue damage and consequently higher surgical stress response when compared with conventional laparoscopic surgery.

As one might expect, Zawadzki and co-workers demonstrate in their prospective study that when compared with open colorectal surgery, robotic colorectal surgery results in a less pronounced inflammatory stress response and hence more pronounced anti-inflammatory action (907). Evidently, open colorectal surgery leads to a more pronounced inflammatory reaction than laparoscopic surgery with or even in spite of the accompanying pneumoperitoneum.

Bedirli and colleagues report that thoracic epidural bupivacaine attenuates the inflammatory response, oxidative injury, and mucosal apoptosis induced by mesenteric ischaemia/reperfusion (in rats) (908).

Interestingly, Singh et al. report that perioperative simvastatin use in major colorectal surgery attenuates the early pro-inflammatory stress response to surgery. In their prospective, double bind, randomized controlled trial, 132 patients were randomly allocated to the simvastatin (S) group or the placebo (P) group. Patients in the S group received 40 mg oral simvastatin once daily for 3 to 7 days preoperatively till 14 days postoperatively. Patients in the P group received a placebo once daily during the same period. Although there were no significant differences between the two groups in the incidence, grade and type of postoperative complications, plasma concentrations of IL-6, IL-8 and TNFα (together with the peritoneal concentrations of IL-6 and IL-8) were significantly lower in the simvastatin group postoperatively (909).

As mentioned previously in the case of thoracotomy, the ON-Q® local anaesthetic–infiltrating catheter has been developed for the treatment of postoperative pain (315,316). 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 anaesthetic to a patient’s surgical site or in close proximity to nerves, providing targeted pain relief for up to five days.

Kim and colleagues have investigated the effects of the ON-Q® on postoperative pain and immune function following laparoscopic resection of colorectal cancer, and compared it with intravenous patient-controlled analgesia (IV PCA). In a prospective, randomized

setting, 60 patients were assigned to either the opioid group (IV PCA receiving fentanyl) or the ON-Q group (continuous wound infiltration of 0.5% ropivacaine and tramadol via IV PCA). There were no significant differences in pain control, natural killer cell cytotoxicity and interleukin-2 levels between both groups. The incidence of postoperative complications and recurrence or metastasis within 1 year after surgery was comparable between the 2 groups. Postoperative inflammatory responses were also similar between the groups. Therefore, the authors conclude that an intravenous fentanyl-based analgesic regimen and a ropivacaine wound infiltration-based analgesic regimen can both be used for postoperative pain management in laparoscopic resection of colorectal cancer (910).
Unfortunately, the effects of the ON-Q on pain and immune function were not compared with the effects of thoracic epidural analgesia in this study. By contrast, Gebhardt et al. have compared thoracic epidural analgesia with ON-Q infiltrating catheters in patients undergoing open thoracotomy. Results showed that patients who received thoracic epidural analgesia had lower average pain (315).

Meyhoff et al. emphasize the importance of the level of inspiratory oxygen fraction during abdominal surgery. 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 (911).

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 (912).

Recent study results suggest that supplemental oxygen does not reduce surgical site infection risk. Furthermore, no increased risk of surgical site infection was observed with the use of a single low dose of dexamethasone. Therefore, the authors conclude that a low dose of dexamethasone (4 mg) can be used for nausea and vomiting prophylaxis without promoting wound infections (913).

By contrast, two other studies in an experimental setting showed oxygen to have suppressing effects on cancer (914,915). 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% (916).

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 traditionally incorporate a potentially greater risk for anastomotic leak after colorectal resection with primary anastomosis (917,918).

Based on the results of their meta-analysis, Mathiesen and co-workers state that anastomotic leakage may be associated with NSAID use (919). However, whether or not epidural analgesia was taken into account is not mentioned.

In turn, Van der Vijver and colleagues have investigated the effects of diclofenac on anastomoses in rats and conclude that immediate postoperative administration of diclofenac and, to a far lesser extent, naproxen might affect healing in the ileal anastomosis in rats. It must be noted that when administration of diclofenac was postponed to day 3 after surgery, anastomotic dehiscence was almost absent. Remarkably, the colonic anastomosis and abdominal wall always remained unaffected. (920).

Yauw and colleagues report similar findings. In their study, involving rats, the use of diclofenac was associated with a greater risk for anastomotic leak in case of anastomosis of the ileum and proximal colon, but not of the distal colon. Delayed treatment with diclofenac

(starting 1 to 2 days postoperatively) also resulted in a substantial decrease in anastomotic leak (921).

Bakker et al., on the other hand, claim that the use of diclofenac (within their enhanced recovery program) is associated with higher risk of anastomotic leakage following elective colorectal surgery. Therefore, the authors state that the use of diclofenac in colorectal surgery can no longer be recommended (922).

Based on the results of their meta-analysis, Peng's group supports the finding that postoperative NSAIDs use, especially nonselective NSAIDs, could increase the incidence of anastomotic leak in patients undergoing gastrointestinal surgery. Also, NSAIDs could decrease postoperative nausea and vomiting, and intestinal obstruction with no effects on cardiovascular events and surgical site infections (923).

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 (924).

Paulasir and co-workers have also performed a retrospective study in which the use of NSAIDs on anastomotic leak risk was investigated. Their results show no increased risk of anastomotic leakage in patients using NSAIDs in the early postoperative period after elective colorectal surgery (925).

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 (926).

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 (927).

By contrast, Haddad and colleagues claim that perioperative NSAID utilization appears to be safe in emergency general surgery patients undergoing small bowel resection and anastomosis. However, NSAIDs should be used cautiously in emergency general surgery patients with colon or rectal anastomoses (928).

Based on the results of their population-based study, Nikolian and co-workers report that male sex, obesity (body mass index > 30 kg/m^2), tobacco use, chronic immunosuppression, thrombocytosis, longer operative duration, and acute/emergency operation represent risk factors for anastomotic leakage. The use of NSAIDs is not mentioned as a risk factor in this study. Moreover, of the 9192 colorectal resections studied, 2.7% had a documented anastomotic leak (929).

Burton and colleagues were also unable to detect any statistically significant difference in incidence of anastomotic dehiscence between NSAID users and non-users (930).
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 (931).

Rutegård et al. have performed a retrospective cohort study involving more than 2600 patients in which the risk of anastomotic leakage following NDAID use was studied in patients undergoing anterior resection for rectal cancer. Their results failed to confirm a positive association between NDAID use and anastomotic leakage. On the contrary, after adjustment for confounding, patients treated at NSAID hospitals had a reduced risk of developing anastomotic leakage (932).

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 (933). 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 (934).

Based on the results of their meta-analysis, Holte and Kehlet conclude that there is no statistically significant evidence from randomized trials to indicate epidural analgesia with local anaesthesic to be associated with an increased risk of anastomotic leakage (935).

Piccioni and co-workers also report that epidural analgesia does not affect the anastomotic leakage risk in an adverse way after open surgery for cancer colorectal cancer (936).

On the contrary, Ryan et al. demonstrate that anastomotic leak rates and death rates were lower in patients anaesthetized with combined general anaesthesia and epidural analgesia compared to general anaesthesia alone. Furthermore, the lowest incidence of anastomotic leak was reported in patients receiving continuous epidural analgesia. Strikingly, an increased incidence of wound dehiscence was reported in patients receiving postoperative epidural analgesia with *morphine* alone (937).

Rojas-Machado and colleagues have performed an extensive survey and meta-analysis to identify potential risk factors for anastomotic leakage for the development of the prognostic index PROCOLE (prognostic colorectal leakage). Apparently, perioperative NSAID use

was not identified as a potential risk factor since NSAID use was not incorporated in the prognostic index (938).

Based on the results of their multicentre observational study, including 7231 consecutive patients undergoing an anterior resection for rectal cancer, Ortiz et al. have identified the following risk factors for anastomotic leakage: male sex, tumour located below 12 cm from the anal verge, and advanced tumour stages. A defunctioning stoma seemed to prevent this complication. Administration of neoadjuvant treatment (NSAID) and/or hospital surgical volume, were not identified as risk factors for anastomotic leakage (939).

Quite the opposite in fact, Reisinger's group claims that COX-2-induced PGE2 production is essential for intestinal wound healing after colonic surgery, possibly via its effects on angiogenesis. Therefore, the authors state that COX-2 inhibitors should be avoided after colonic surgery, and that administration of PGE2 might be favourable for a selection of patients (940).

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 (941). 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 (941).

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 (942). Shekarriz et al. support this finding. In their study, neoadjuvant radiotherapy was not associated with a higher risk for developing anastomotic leakage following colorectal surgery. Interestingly, the anastomosis technique used by the surgeon proved to be significantly associated with anastomotic leak. Patients in whom side-to-end anastomosis technique was used were significantly less likely to develop anastomotic leakage compared with patients patients in whom end-to-end anastomosis technique was used. NSAID use was not identified as a risk factor for anastomitic leakage following colorectal surgery (943).

Zakrison and colleagues, in their turn, identified the perioperative use of vasopressors as a risk factor for gastrointestinal anastomotic leakage. They report that vasopressors appear to increase anastomotic leaks threefold, independent of clinical/surgical status or hypotension (944).

Jestin et al. have performed a retrospective case-control study in which risk factors for anastomotic leakage following rectal cancer surgery were investigated. They report that the most important risk factors for leakage were adverse intraoperative events, low anastomoses and preoperative radiotherapy. In this study, a diverting stoma appeared protective. Postoperative epidural analgesia, however, had no significant beneficiary effect on anastomotic leakage (945).

Lim and colleagues point out that late anastomotic leakages that develop after 30 days following low anterior resection are not uncommon and may be associated with the use of radiotherapy. Diverting stoma had no protective effect on late leakages in their study (946).

Marinello and co-workers state that the individual surgeon is an important risk factor for anastomotic leaks. In their retrospective analysis involving over 1000 patients, the individual surgeon and perioperative blood transfusion were identified as significant risk

factors for the development of anastomotic leakage. Therefore, the authors conclude that efforts should be made in order to reduce performance variability amongst surgeons (947).

Käser and co-workers claim that distant metastasis in colorectal cancer is a risk factor for anastomotic leakage. In their retrospective cohort study, stage IV colorectal cancer was significantly associated with an increased anastomotic leakage rate following surgery compared with stage I-III colorectal cancer. Diabetes also proved to be significantly associated with an increased risk of anastomotic leakage. The use of NSAIDS, on the other hand, was not associated with an increased risk of anastomotic leakage (948).

Rushfeldt et al. have performed a propensity score analysis in which the effects of perioperative use of dexamethasone and different NDAIDs on anastomotic leakage risk were analyzed. Results showed that perioperative use of NSAIDs and dexamethasone is not associated with higher risk of anastomotic leak. On the contrary, perioperative use of dexamethasone was associated with a non-significant reduced risk of anastomotic leak. Risk was increased for malignancy, use of vasopressors, blood transfusions, and regular use of steroids. Therefore, the authors conclude that other factors than perioperative drugs are crucial for risk of anastomotic leakage (949).

Slim and colleagues have recently performed a review and meta-analysis on this subject and conclude that the balans of benefit versus risk (analgesic effect/risk of anastomotic disruption) is acceptable. Based on their results, it appears that a prescription of NSAIDs for 48 hours after surgery may be recommended for elective colonic surgery. Nevertheless, the authors state that it is important to respect the specific contra-indications of NSAIDs and avoid postoperative NSAID use if there are risk factors for anastomotic leakage: advanced age, malnutrition, severe co-morbidities and/or intra-operative difficulties (950). According to our opinion, non-elective surgery could be included as a contra-indication for NSAID use following colorectal surgery. Also, it has to be mentioned that any possible beneficiary effects of NSAID use on cancer growth were not included in this benefit/risk equation.

In turn, Duraes et al. state that age plays an independent role in affecting mortality when complications occur following colorectal cancer surgery. In this study, postoperative

morbidity disproportionally increased 1-year mortality in octogenerians when compared to the younger age groups. Anastomotic leakage, abdominopelvic abcesses, reoperation, and readmission rates were comparable among the different age groups, but were associated with a disproportionate risk of 1-year mortality in octogenerians. Besides these, American Society of Anesthesiologists (ASA) and pathological state III were additional independent variables associated with 1-year mortality (951).

Shakhsheer et al. claim that morphine promotes the colonization of anastomotic tissue with collagenase-producing enterococcus faecalis, thus causing anastomotic leakage. The authors conclude that these results provide further rationale to enhanced recovery after surgery (i.e. ERAS) programs that suggest limiting or avoiding the use of opioids in gastrointestinal surgery (952).
The same group also reports that tissue hypoxia is not a distinctive feature of anastomotic tissues that fail to heal and leak, even when their blood supply is interrupted (953).
Since anastomotic leaks can be caused by intestinal pathogens that produce collagenase, Hyoju and colleagues have investigated the effects of polyphosphate administration on the development of anastolotic leaks. Results showed that oral phosphate administration suppressed bacterial collagenase production and prevented anastomotic leak caused by Serratia marcescens and Pseudomonas aeruginosa. Based on the results of this study in mice, they conclude that polyphosphate administration may be an alternative approach to prevent anastomotic leakage induced by collagenolytic bacteria with the advantage of preserving the intestinal microbiome and its colonization resistance (954).

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.

With respect to anastomotic leaks, Zawadzki et al. report that C-reactive protein (CRP) and procalcitonin (PCT) measurement on the third postoperative day following colorectal cancer resection can positively identify patients at low risk of anastomotic leakage (955).
Sammour’s group, on the other hand, claims that peritoneal levels of IL-6 and IL-10 on the first postoperative day following colorectal surgery might predict clinically important anastomotic leak (956).

Mik et al. support the idea that routine measurement of CRP can help to make an earlier diagnosis of intra-abdominal septic complications and earlier decision for laparotomy (957). The same group also reports that CRP and NLR (on the 4th postoperative day) possess the ability to predict the development of anastomotic leak and postoperative mortality after colorectal cancer surgery. A CRP > 180 mg/L and NLR > 6.5 were significantly associated with anastomotic leakage and increased mortality (958).

In this context, Holl and colleagues claim that in case an elevated CRP is found on the 4th postoperative day, an abdominopelvic CT scan should be performed to rule out the existence of intra-abdominal complication. Needless to state, a normal result does not formally eliminate the existence of intra-abdominal complications (959).

Interestingly, Haskins' group states that bowel preparation is not associated with worse patient outcomes in those patients with an established anastomotic leak following elective colon surgery with primary anastomosis (960).

Xu et al. have conducted a prospective, double blind, placebo-controlled study in which the effects of perioperative intravenous flurbiprofen (NSAID) on bowel function were investigated. Their results reveal that the combination of perioperative intravenous flurbiprofen, intraoperative thoracic epidural anesthesia, and postoperative patient-controlled epidural analgesia facilitated recovery of bowel function, enhanced analgesia, and attenuated the cytokine response (961).

Furthermore, evidence is growing that inflammation plays a key role in colon carcinogenesis, and that NSAIDs, like diclofenac, may display chemopreventive effects. Ghanghas et al. demonstrate that the administration of NSAIDs significantly reduces the inflammatory potential of a growing neoplasm (962).
Paunescu and colleagues even report that NSAIDs like diclofenac are currently being modified, especially for their anticancer properties (963).

As mentioned previously, the perioperative use of epidural analgesia also has been shown to have a beneficiary effect on anastomotic leakage (607,608). 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 (136-140).
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 at least inconsistent 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 conjunction with thoracic epidural analgesia should be evaluated on an individual basis (964). In case of a high preoperative NLR, we would advise to initiate treatment with NSAID's 24 hours postoperatively (925). 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 (965). 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 (966).

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 that 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 (967).
Based on the results of their meta-analysis, Lu et al. confirm that cancer-specific mortality and local recurrences are higher in patients with anastomotic leak compared to patients without anastomotic leak (968).

Interestingly, Govaert and colleagues have performed a retrospective analysis of clinical and financial outcomes after colorectal cancer surgery in 29 Dutch hospitals. They report that complications after colorectal cancer surgery are associated with a substantial increase in costs. Of the total hospital costs, 31% was spent on complications. Independent from other risk factors, ASA IV, double tumour, ASA III, short course preoperative radiotherapy and TNM-stadium disease were the top-5 attributors to high costs (969).

Igarashi et al. even suggest that epidural analgesia might reduce the risk of surgical site infection by increasing the expression of lipocalin-2 and decreasing the expression of E Coli DNA at pseudosurgical sites in sick but not healthy rats (970).

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 (110-114,971-973).

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's 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 (974).

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 (975).

Lönnroth and colleagues confirm the relation between NSAID use and colorectal cancer. They report that standard oral administration of NSAID's for three days preoperatively to patients with colorectal cancer changes tumour mRNA and protein expression in a biologically favourable direction. Expression of several genes responsible for growth, invasion and metastasis is decreased, whilst expression of tumour suppressors is increased, and the immune system is activated (976). This change towards less aggressive tumour cells may thus be associated with improved outcome in patients (977).

With respect to the possible mode of action, Rana and co-workers report that the downregulation of telomerase activity by diclofenac and curcumin is associated with cell cycle arrest and induction of apoptosis in colon cancer cells (978).

For further information regarding the role of telomerase and cancer growth we refer to the paper published by Shayl et al. (979).

Ye et al. have conducted a meta-analysis of observational studies in which the relationship between aspirin use after diagnosis of colorectal cancer and patient survival was studied. Their results show that the use of aspirin after diagnosis was associated with reduced all-cause mortality for colorectal patients. However, colorectal cancer-specific mortality was not influenced by the use of aspirin. Interestingly, subgroup analysis revealed that aspirin use was associated with longer survival among patients with the variant PIK3CA gene but not for those with wild-type PIK3CA (980).
The PIK3CA gene provides instructions for making the p110 alpha (p110α) protein. Mutations in the PIK3CA gene are involved in many types of cancer, including cancer of the ovary, breast, lung, brain, and stomach. These mutations are also involved in colorectal cancer. The PIK3CA gene mutations involved in cancer are somatic, which means they are acquired during a person's lifetime and are present only in the tumor cells. These mutations change single amino acids into the p110α protein.
Cancer-associated PIK3CA gene mutations result in production of an altered p110α subunit that allows PI3K to signal without regulation. The increased signaling leads to abnormal proliferation of cells, resulting in the development of cancer (981).

Based on the results of their population-based case-control study, Friis et al. report that long-term continuous use of low-dose aspirin and long-term use of nonaspirin NSAIDs are associated with reduced colorectal cancer risk (982).

On the other hand, Cardwell and his group were unable to detect any relation between aspirin use and improved survival in colorectal cancer patients. In their population-based case-control cohort study, low dose aspirin use after a diagnosis of colorectal cancer was not associated with colorectal cancer-specific mortality (983).

Burr et al. report that there is lack of high quality evidence suggesting that aspirin or non-aspirin non-steroidal anti-inflammatory drugs can prevent colorectal cancer in inflammatory bowel disease (984).

By contrast, Dulai's group has performed a system review and meta-analysis in which the chemopreventive action of NSAIDs on colorectal cancer was investigated. Their results show that among individuals with previous colorectal cancer, non-aspirin NSAIDs are the most effective agents for the prevention of advanced metachronous neoplasia, whereas low dose aspirin has the most favourable risk/benefit profile (985).

Tougeron and co-workers expand further on the relation between aspirin use and colorectal cancer (986).

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 (157).

Özgehan and colleagues claim that the preoperative NLR can be used as a valuable predictive parameter in patients with colorectal cancer. This claim is based on the results of their retrospective study, in which NLR was significantly associated with tumour stage (987).

Rashtak et al. state that NLR is an independent prognostic variable for non-metastatic colon cancer that enhances existing clinical staging systems (988).

Kennelly's group demonstrates that prognosis in colon cancer is intimately linked to the patient's immune response. In this study, NLR $\geq$ 4.0 was significantly associated with node positive disease (989).

Emir et al. conclude that NLR and PLR may be used for follow up conversion of colonic and rectal neoplastic polyps to invasive tumour. This conclusion is based on the fact that NLR and PLR were significantly higher in patients with colorectal cancer compared to patients with colorectal polyps and healthy individuals. There was no difference in NLR and PLR between healthy individuals and patients with colorectal polyps. In this study the optimum NLR cut-off point for neoplastic polyps was 2.28 (990).

Azab and co-workers confirm the importance of the pre-treatment NLR in predicting the long-term survival in colorectal cancer. 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 (991).

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 (992).

Choi and colleagues confirm the prognostic value of preoperative NLR in patients undergoing resection for non-metastatic colorectal cancer. In their study, a high NLR (≥ 2.6) was significantly associated with worse recurrence free survival and overall survival (993).

Wu and co-workers support the prognostic properties of NLR and PLR in patients with colorectal cancer and synchronous liver metatsasis. In their retrospective study, NLR < 4.0 and PLR < 150 correlated significantly with better disease control (palliative resection followed by oxaliplatin-based chemotherapy) (994).

In turn and based on the results of their retrospective study, Oh cum suis claim that among the systemic inflammatory markers, NLR is a strong predictor of worse disease-free survival and overall survival in stage II colorectal cancer (995).

Based on the results of their meta-analysis, Tsai et al. conclude that NLR and carcino-embryonic antigen (CEA) are valuable tools for the prediction of prognosis in colorectal cancer and adjustment of treatment strategy. Patients with NLR < 5.0 before treatment were significantly more likely to have 5-year overall survival and 5-year disease-free survival. Pretreatment CEA level < 5.0 was significantly associated with complete tumour response and tumour downstaging after neoadjuvant treatment. Furthermore, patients with NLR > 5.0 had a larger tumour, poorer tumour differentiation, and higher CEA level (996).

Mahsuni Sevinc and colleagues report that preoperative levels of CEA, albumin, PLR, and NLR have significant prognostic value for patients with colorectal cancer undergoing surgery (997). However, in multivariate analysis only albumin retained its significance.

Passardi et al. support the prognostic value of pretreatment NLR as a predictor of prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer (998).

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 (999).
Apparently, in this study a high NLR before chemotherapy appears to be associated with more aggressive disease and (potentially) worse outcome. By contrast, a high NLR after chemotherapy appears to be associated with better outcome.

As discussed earlier, Teo et al. reported similar findings (815). 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 (808). 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 (1000).

Turner et al. report similar findings. Based on the results of their study, in which they have examined the effect of primary tumour resection on systemic inflammation and survival in patients with metastatic colorectal cancer, they claim that reversal of an elevated NLR after surgery (> 5.0) is associated with significantly improved overall survival (1001).

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 (1002).

Prete et al. also conclude that high NLR is associated with worse overall survival in patients with colorectal cancer receiving regorafenib (1003).

Nagasaki and co-workers endorse the prognostic significance of NLR in patients with advanced low rectal cancer treated with preoperative chemoradiotherapy. In their study, a high NLR (≥ 3.0) prior to neoadjuvant chemoradiotherapy and followed by surgery was independently associated with poor prognosis (1004).

However, Lino-Silva et al. have performed a retrospective study in which the prognostic significance of NLR in rectal cancer patients with preoperative chemoradiotherapy was

investigated. In this cohort, NLR was not associated with disease-specific survival and did not correlate with pathologic complete response (1005).

Galizia and colleagues report that NLR is a strong predictor of tumour recurrence in early colon cancers. In their propensity score-matched analysis, a high NLR (> 2.36) was an independent prognostic factor of worse prognosis and shorter disease-free survival (1006).

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 (1007).

Based on their prospective cohort study, Cook and co-workers claim that postoperative NLR predicts complications following colorectal surgery. Elective colorectal resection was associated with an increase in mean NLR from 3.5 to 11.6. Patients with a NLR ≥ 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 (1008).

Miyakita's group has also investigated the prognostic value of NLR in predicting complications following radical rectal cancer surgery. Their results show that NLR was an independent risk factor for anastomotic leakage and the only score that could be evaluated before surgery (1009).

Forget and colleagues confirm that NLR correlates more than C-reactive protein with postoperative complications after major abdominal surgery. An increased NLR at the seventh postoperative day was significantly associated with more complications during the first postsurgical month. CRP, on the other hand, showed no correlation (1010).

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 (1011).

Finally, Tohme's study results indicate that NLR is also prognostic for survival in case of radio embolization for metastatic colorectal cancer (1374).

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 (1012).
Pine and co-workers support the predictive value of NLR in patients with colorectal cancer. In their retrospective study, a high NLR (≥ 5.0) significantly predicted lower overall survival and greater disease recurrence (1013).

Kim et al. have studied the predictive value of NLR in patients with rectal cancer undergoing preoperative chemo radiation. 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 (1014).

Zou's group confirms the prognostic value of NLR and PLR in patients with colorectal cancer. In their retrospective study, a high NLR (≥ 4.98) and/or PLR (≥ 246) were significantly associated with worse 5-year overall survival. NLR and PLR were independent prognostic factors in these patients, and were associated with the T classification, lymph node metastasis and postoperative adjuvant chemotherapy response. Postoperative adjuvant

chemotherapy improved the 5-year overall survival rate in patients with a high NLR or PLR. Furthermore, NLR proved more effective as a prognostic marker compared with PLR (1015).
Although a high NLR is associated with worse outcome, it also appears to be associated with a favourable response to therapy. In this case with adjuvant chemotherapy, but also with anti-inflammatory treatment in breast cancer patients, as described previously by Forget and colleagues (137).

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 chemo radiation in patients with locally advanced rectal cancer. In this retrospective study, a NLR < 2.8 was significantly associated with better overall survival (1016).
These findings are confirmed by another meta-analysis performed by Paramanathan et al. (151).

Toiyama and colleagues confirm the importance of NLR in rectal cancer patients after neoadjuvant chemotherapy. Elevated NLR was clearly associated with significantly poor overall survival, but so was elevated platelet count (PLT) (1017).

Ghanim et al. have investigated the prognostic impact of inflammatory-related biomarkers and scores in patients undergoing curative pulmonary metastasectomy for colorectal cancer. They conclude that inflammatory markers provide promising prognostic information in this group of patients (1018).

Zhou, Chu and An conclude that difference of leucocyte count, neutrophil ratio, and NLR may provide available information in the differential diagnosis of colorectal cancer, adenomatous polyp and healthy people. In their prospective and randomized study, NLR was highest in the colorectal cancer group, the second in the adenomatous polyp group, and the lowest in the healthy control group (1019).

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 (1020).

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 (1021).

Wuxiao and Chen confirm the importance of NLR as a prognostic tool in patients with colorectal cancer. Wuxiao and colleagues have developed a prognostic model based on histological grade, pre-treatment carcinoembryonic antigen (CEA) and NLR levels (1022).

Chen et al. have performed a retrospective analysis on multiple cohorts of colorectal cancer patients: metastatic untreated, refractory metastatic, hepatectomy, stage II-III and molecularly screened. Results showed that high NLR (> 5.0) was associated with poor prognosis in patients with metastatic colorectal cancer. Furthermore, high NLR correlated with increased expression of interleukin-6, interleukin-8, interleukin-2Rα, hepatocyte growth factor, macrophage-colony stimulating factor, and vascular epidermal growth factor. Another fourteen additional cytokines were reported to correlate with high NLR. All cytokines fell into three major clusters: inflammatory cytokines, angiogenic cytokines, and epidermal growth factor ligands (1023).

Watt and co-workers have investigated the importance of the differential white cell count in patients undergoing elective surgery for colorectal cancer. Based on the results of their retrospective study, they claim that the neutrophil count is the most important prognostic component of the differential white cell count (WCC). Of the components of the differential WCC, only the neutrophil count proved independently associated with survival, particularly in node-negative colon cancer (1024).

Shibutani et al. have studied the relationship between survival/chemotherapeutic response and pre-/post-treatment markers of systemic inflammation (NLR, CRP and GPS (Glasgow Prognostic Score)) in patients with unresectable metastatic colorectal cancer. Their results showed significantly worse overall survival in the group with high pre-treatment inflammatory markers (NLR/CRP/GPS), and that with high post-treatment CRP/GPS. Progression-free survival rate was significantly worse in the high post-treatment CRP group. With respect to chemotherapeutic response, patients with a low post-treatment CRP level had a significantly higher disease controle rate than those with a high post-treatment CRP level. Furthermore, patients with a high pre-treatment CRP level and normalization after treatment showed better overall and progression-free survival rates and had a significantly higher disease control rate than those with high pre- and post-treatment CRP levels (1025).

As mentioned previously with respect to lung (371), oesophageal (638) and hepatocellular cancer (807), Chen and co-workers claim that the systemic immune-inflammation index (SII) is a powerful tool for predicting survival outcome in patients with colorectal cancer. In their study, SII was calculated using the formula SII = (PxN/L), where P, N, and L refer to peripheral platelet, neutrophil, and lymphocyte counts, respectively (1026).

Chan’s group reports that lymphocyte-to-monocyte ratio, but not NLR, is associated with better overall survival in patients with resectable colorectal cancer (1027).

Interestingly, Sun and colleagues claim that pre-treatment 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 (1028).
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 tumour 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 tumour cells.
For more comprehensive information on the role of fibrinogen on cancer development we refer to the paper by Sun et al. (1028).

Hong et al. support the finding that preoperative fibrinogen levels represent a prognostic factor in non-metastatic colorectal cancer. In this prospective cohort study, plasma fibrinogen, but not D-dimer, was identified as a prognostic factor (1029).

As mentioned previously, Arigami and co-workers conclude that the combination of fibrinogen concentration and NLR may be a potentially useful blood marker for predicting tumour progression and the prognosis of patients with gastric cancer (774).

Interestingly, Hollmann and colleagues have studied the effects of epidural analgesia on coagulation in patients undergoing major orthopaedic surgery. The results of their study revealed that use of epidural analgesia prevents immediate postoperative hypercoagulability without affecting physiologic aggregation and coagulation processes (1030).

There is clear evidence that cancer and blood clotting are tightly connected. Cancer cells have the ability to up regulate specific blood clotting factors and this is believed to result in the formation of unwanted blood clots in veins and the lungs, often leading to fatal, thrombotic complications in cancer patients (1031). From this point of view, the use of epidural analgesia may thus have a beneficiary effect on coagulation in surgical cancer patients.

Mariani et al. expand further on the significance of inflammation in the development of colorectal cancer (1032). 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. attenuation, 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 phagocytized 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 (1033). 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 haemostasis, 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 up regulated 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 (1034).

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 leukotrienes have been shown to be linked to early colon cancer growth and proliferation (1035).

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 (1036,1037).
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 (1038).

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 (1032). 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 (1032).

Zou's group suggests that IL-35 (an immunosuppressive cytokine) can promote tumour progression by functioning as an up-stream cytokine to promote cancer-associated inflammation and control neutrophil polarization (1039).

Moore and Pidgeon expand further on the importance of the 5-lipoxygenase pathway in tumorigenesis and discuss the potential routes through which cancer cells may utilize this pathway to interact with the tumour microenvironment during the development and progression of a tumour (1040).

Lalmahomed et al.'s study results support the abovementioned mechanisms of action. Although 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 body's 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 (1041).

Nonetheless, Seeberg et al. claim that circulating tumour cells in patients with colorectal liver metastases predict non-resectability and impaired survival (1042).

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 heterogeneous 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 (1043).

Granot and Jablonska expand further on the role of neutrophils in cancer. In summary, neutrophils appear not to be a homogeneous population of cells and may consist of both pro- and antitumour subpopulations. Furthermore, depending on the tumour microenvironment, neutrophils polarize toward a tumour promoting or an antitumour phenotype, wich is mediated via cytokines present in the tumour microenvironment (1044).

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 also found to exhibit relatively poor cancer-killing activity compared to the cytolytic activity of the average healthy donor (1045).

Tohme and co-workers claim that neutrophil extracellular traps (NET), which are formed when neutrophils expel their protein-studded chromatin in response to surgical stress, promote the development and progression of liver metastases following surgery (1046).

Richardson's group reports to have identified a novel neutrophil phenotype demonstrating reduced NET formation, reduced apoptosis, and increased phagocytosis in patients undergoing colorectal cancer resection. As a consequence of impaired cell death, accumulation of neutrophils in the circulation could potentially be harmful to the host following surgery (1047).

Gryglewski and Szczepanik state that surgery results in decreased percentage of Tγδ lymphocytes in peripheral human blood, and this decrease correlates with the severity and location of the surgical trauma (1048).

Meanwhile, Wikberg and co-workers report that low infiltration of neutrophils in the tumour front is an independent prognostic factor for a poorer patient prognosis in early stages of colon cancers (1049).

Rahat et al. and Yang et al. expand further on the role of macrophages and neutrophils in the regulation of the inflammatory microenvironment in cancer and autoimmunity (1050,1051).

Tabuchi and colleagues have conducted a prospective study, in which patients with colorectal cancer undergoing surgical resection were studied in relation to pre- and postoperative granulocyte/lymphocyte ratio (GLR) and pro- and anti-inflammatory cytokines. Results revealed that serum interleukin-6 (IL-6) was higher on the first postoperative day compared to before the operation. GLR was also higher on the first 3 postoperative days compared to beforte the operation and gradually decreased together with the surgical stress levels. GLR and the number of granulocytes in the blood showed significant correlation with IL-6. By contrast, GLR and the number of granulocytes and lymphocytes in the blood showed no correlation with serum IL-1β or TNF-α. Therefore, the authors conclude that GLR appears to be a simple and clinically relevant parameter for the assessment of perioperative stress in patients undergoing colorectal surgery (1052).

The recently published study results by Navarro and co-workers support the importance of inflammation in colorectal and lung cancer. Epidemiologic findings suggest that long-term use of the non-vitamin dietary supplements glucosamine and chondroitin is associated with

reduced risk of colorectal and lung cancer. Navarro et al. demonstrate that the use of these dietary supplements for 28 days (compared to placebo) significantly reduces inflammatory markers. This finding adds additional evidence for the association between inflammation and these cancers (1053).

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 anaesthetic 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 patients received postoperative analgesia with morphine as a patient-controlled analgesia (1054). Needless to mention, any pre-emptive mode of action has been ruled out by the administration of the blocks at the end of surgery.

In turn, Pedrazzani et al. have compared the effects of TAP blockade plus local wound infiltration with local wound infiltration alone on opioid requirement in patients undergoing laparoscopic colorectal surgery within an ERAS program. Not surprisingly, the combination of TAP blockade and local wound infiltration reduced the requirement of opioid analgesics and resulted in good pain control (1055).

Tikuisis and colleagues endorse the analgesic properties of ultrasound-guided TAP blockade in patients undergoing hand-assisted laparoscopic colon surgery. In their prospective, randomized, placebo-controlled trial, TAP blockade (using 20 mL of 0.375% ropivacaine) significantly reduced pain, short-term postoperative analgesic use and promoted early ambulation when compared to placebo. The TAP block group had significantly lower pain scores after surgery at 2, 4, and 12 hours at rest, and at 2 and 4 hours during movement (1056).

Based on the results of their systematic review and meta-analysis of randomized trials, Brogi's group concludes that TAP blockade can play an important role in the management of pain after abdominal surgery by reducing both pain scores and 24-hour morphine consumption, especially when neuraxial techniques or opioids are contraindicated (1057).

Arora's group supports the finding that TAP block reduces postoperative pain up to 24 hours compared to port-site infiltration in patients undergoing laparoscopic inguinal hernia repair (1058).

Based on the results of their meta-analysis, Kim and co-workers state that TAP blocks are easily performed, cost-effective, and an opioid-sparing adjunct for laparoscopic colorectal surgery, with minimal procedure-related morbidity (1059).
El-Sherif et al. conclude that the addition of morphine to bupivacaine in TAP blocks is an effective method for pain management in patients undergoing abdominal cancer surgery without serious side-effects (1060).

However, Torup and colleagues report that TAP block used in combination with paracetamol and ibuprofen did not reduce pain after laparoscopic colonic surgery. Although pain was not reduced, there was a 30% reduction in opioid use in the first postoperative hour. These conclusions are based on the results of their randomized, placebo-controlled, double blind study (1061).

Oh et al. also failed to demonstrate any beneficial effect of TAP blockade on postoperative pain in colorectal cancer patients undergoing laparoscopic colorectal surgery. In this double blind, randomized and controlled trial, pain intensity on coughing and at rest in all studied time periods did not significantly differ between the group that received TAP block with bupivacaine and the group that was injected with saline. Furthermore, there were no significant differences in postoperative opioid consumption, sedation scores, nausea scores, complication rates, and length of hospital stay between the two groups (1062).

Tupper-Carey et al. have conducted a prospective, randomized trial in which the analgesic efficacy of untrasound-guided TAP block in adult patients undergoing laparoscopic

appendectomy was investigated. Their results show that the additional TAP block performed immediately prior to skin incision (bilaterally 20 ml of plain ropivacaine 0.5%) for laparoscopic appendectomy did not significantly improve postoperative analgesia outcomes (1063).

Based on the results of their meta-analysis, Baeriswyl and colleagues conclude that ultrasound-guided TAP block provides marginal postoperative analgesic efficacy after abdominal laparotomy or laparoscopy and caesarean delivery (1064).

In their review, Jakobsson et al. state that the effects of TAP blockade during laparoscopic cholecystectomy appear to be equivalent to local infiltration anaesthesia and that they also seem to be beneficial during laparoscopic colon resection. These effects are more pronounced when TAP blockade is provided prior to surgery. Therefore, TAP blockade seems an interesting alternative in patients where epidural or spinal anaesthesia/analgesia is technically difficult and/or poses a risk (1065).

Niraj and co-workers have investigated the effects of four-quadrant TAP blockade in patients undergoing abdominal surgery in whom epidural analgesia was contraindicated or refused. They report that surgical incision was within the dermatomal limit of the block in 70% of the patients. However, therapeutic failure with this technique was reported to be 10% (1066).

Based on the results of their randomized and placebo-controlled trial, Qazi et al. claim that TAP block produces effective and prolonged postoperative analgesia (up to 24 hours) in patients undergoing midline colorectal surgery. Bilateral TAP blocks (with 20 ml 0.2% ropivacaine on either side) resulted in a considerable reduction in mean intravenous tramadol requirements, reduced postoperative pain scores, and increased time to first request for further analgesia, both at rest and on movement (1067).

Shaker’s group has prospectively compared the analgesic effects of TAP blocks with thoracic epidural analgesia in patients undergoing major abdominal resections. In contrast with other studies, their results suggest that TAP block use is associated with lower

parenteral morphine equivalent usage and decreased incidence of hypotension in the early postoperative period compared with thoracic epidural analgesia. There was no difference in 24-48 hour fluid balance, and/or subjective pain between the two groups (1068).

Park et al. report that their newly introduced laparoscope-assisted TAP (LTAP) block is non-inferior to the ultrasound-guided technique in providing a TAP block after colorectal surgery. With the LTAP local anaesthetics are injected intraperitoneally (1069).

Bashandy and Elkholy have studied the effects of an ultrasound-guided pre-emptive 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 (1070).

However, Purdy et al. report that (post-surgery) placement of a rectus sheath block does not significantly reduce the inflammatory response in patients undergoing midline laparotomy. In their prospective randomized study, rectus sheath blockade had no significant effect on the inflammatory biomarkers (CRP, IL-1ra, IL-6, IL-8, IL-10, and IL-1β). Interestingly, NRS score was significantly correlated with plasma concentrations of the anti-inflammatory cytokine IL-10 and pro-inflammatory cytokine IL-1β postoperatively. This finding clearly suggests that inflammation and pain are related (1071). With respect to the inflammatory response, previous studies have shown that pre-emptive analgesia has more impact on the inflammatory stress response than postoperative interventions (79,302). This could explain why post-surgery blockades have little impact on the inflammatory response.

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 (1072).

As mentioned previously, Shah and colleagues demonstrate that intraoperative continuous epidural infusions decrease PACU length of stay as discharge criteria for patient-reported pain scores are met earlier (306).

Based on the results of their systematic review of randomized controlled trials, El-Boghdadly and co-workers conclude that thoracic paravertebral blockade (TPVB) appears to be a promising analgesic technique for abdominal surgery in terms of efficacy and safety (1073).

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 (1074).

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 (1075).

Giampieri and co-workers confirm that in patients with metastatic colorectal cancer, who were treated with first-line chemotherapy, β-blocker use was associated with improved overall survival. However, in patients treated with first-line chemotherapy in combination with bevacizumab β-blocker use was not associated with improved overall survival. On the contrary, in this patient group a trend was observed toward a worse overall survival (1076).

As mentioned previously in the case of head and neck cancers and based on the results of their population-based cohort study, Chang and co-workers state that propranolol might reduce the risk of head and neck, oesophagus, stomach, colon and prostate cancers (275). However, Numbere et al. were unable to confirm any protective effect of β-blockade on bowel cancer risk. In their case-control study, adrenergic blocker use was not associated with a reduced risk of bowel, breast, lung and/or prostate cancer (387).

However, Hicks and colleagues were unable to detect any relation between post-diagnosis beta-blocker use and decreased mortality in patients with colorectal cancer. In their nested case-control study, beta-blocker use was identified in 21.4% of 1559 colorectal cancer-specific deaths and 23.7% of their 7531 matched controls (1077).

Based on the results of their population-based study, Jansen and co-workers were also unable to detect any beneficial effect of pre- or post-diagnosis beta-blocker use on colorectal cancer prognosis (1078).
In fact, these authors claim that immortal time bias leads to spurious beneficial associations of beta-blocker use among cancer patients (1079). Immortal time refers to a period of follow-up during which, by study design, death or the study outcome simply cannot occur (1080).

Nevertheless, Ciurea's group reports that β2-adrenergic receptors play an important role in colorectal carcinogenesis and can be used as prognostic factors. This conclusion is based on the fact that β2-adrenergic receptors were significantly associated with tumour grading, tumour size, tumour invasion, and lymph node metastasis (1081).

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 (1082).

Chin and co-workers claim that selective β2-adrenergic blockage suppresses colorectal cancer growth in vitro and in vivo (1083).

Sorski and co-workers have investigated whether blocking excess release of endogenous catecholamines and prostaglandins during surgical procedures of different extent can reduce experimental liver metastasis of colon cancer in mice. Their results show that combined administration of propranolol and etodolac, but neither drug alone, significantly improved host resistance to metastasis. These beneficial effects occurred in both minor and extensive surgeries, and in both male and female mice. Therefore, the authors conclude that given the prevalent perioperative psychological and physiological stress responses in patients, and ample prostaglandin release by colorectal tumours and injured tissue, propranolol and etodolac should be tested clinically in laparoscopic and open colorectal surgeries in an attempt to reduce patients' metastatic disease (1084).

As mentioned previously in the case of non-small cell lung cancer and pancreatic cancer, resting heart rate appears to be associated (independently of haemoglobin level and tumour stage) with survival in patients with advanced colorectal cancer (391).

Interestingly, Singh et al. have performed a prospective, double blind, randomized controlled trial in which the effects of perioperative simvastatin therapy on the systemic inflammatory respons following major colorectal surgery were investigated. Results revealed that perioperative simvastatin therapy attenuates the early pro-inflammatory stress response to surgery. However, simvastatin therapy had no effect on postoperative complications (1085).

And 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 (966).

Boland et al. claim that intraoperative fluid infusion volumes in excess of 3500 ml are associated with increased morbidity and length of stay in patients undergoing elective surgery for rectal cancer. This claim is based on the results of their retrospective study (1086).

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, hypocalcaemia, hypomagnesaemia, worse acid-base equilibrium and higher level of neutrophil gelatinase-associated lipocalin. Therefore, the authors conclude that the use of balanced solutions was responsible for less alteration of plasmatic electrolytes, acid-base equilibrium, kidney function and that it might be associated with an early anti-inflammatory mechanisms triggering (1087).

However, it has to be mentioned that, according to Li et al.'s study results, the administration of ≥ 2.0 liters Ringer's lactate prolongs the gastrointestinal recovery time in patients undergoing laparoscopic cancer surgery. By contrast, the administration of ≥ 1.0 liter of hydroxyethyl starch (Voluven) did not adversely affect gastrointestinal recovery (1088).

Behman and colleagues support the concept that increased early perioperative fluid resuscitation is associated with major adverse events in patients undergoing laparotomy, respectively pancreaticoduodenectomy (1089).

Although the use of dexamethasone is claimed to have beneficial effects on recurrence, mortality, and/or postoperative pain in breast, gastric, pancreatic and ovarian cancer patients (404,737,821,1211), Yu and colleagues caution its use in surgical patients with rectal

cancer. Based on the results of their retrospective study, the authors claim that patients not given dexamethasone had better three-year survival outcomes compared with patients given dexamethasone perioperatively (1090). Unfortunately, the reason for dexamethasone use was not mentioned.

Fares et al. have performed a randomized double blind study in which the intraperitoneal administration of dexmedetomidine was investigated in relation to pain and analgesics consumption in patients undergoing laparoscopic colorectal cancer surgery. Patients were randomly assigned for intraperitoneal administration of either 50 ml saline (control group), 50 ml bupivacaine 0,25% (bupivacaine group), or 50 ml bupivacaine 0,25% with dexmedetomidine 1 µg/kg (bupidex group). Results revealed that pain score was significantly reduced during the first 24 hours postoperatively in the bupidex group in comparison to the control and bupivacaine group. Furthermore, mean total consumption of rescue analgesia was significantly reduced and the time to first analgesic requirement was significantly prolonged in the bupidex group. The authors therefore conclude that intraperitoneal administration of dexmedetomidine 1 µg/kg combined with bupivacaine improves the quality and the duration of postoperative analgesia and provides an analgesic sparing effect compared to bupivacaine alone without significant adverse effects in patients undergoing laparoscopic colorectal cancer surgery (1091).

Chen’s group has prospectively investigated the effects of additional dexmedetomidine on gastroinstestinal motility following laparoscopic resection of colorectal cancer. In this randomized, double-blinded study, additional dexmedetomidine (1 µg/kg bolus and 0.3 µg/kg/h as maintenance) was significantly associated with shorter time to postoperative first flatus, shorter time to regular diet, and shorter hospital stay (1092).

Panchgar and colleagues report similar findings. In their prospective, randomized, double blind, controlled trial, dexmedetomidine infusion (1 µg/kg bolus over 10 minutes and 0.5 µg/kg/h intraoperatively as maintenance) controlled the hemodynamic stress response in patients undergoing laparoscopic surgery. Its use also extended the pain free period postoperatively and thereby reduced total analgesic requirement (1093).

In turn and based on the results of their randomized and controlled study, Gao cum suis report that the combination of dexmedetomidine and sufentanil for patient-controlled intravenous analgesia (PCIA) following abdominal surgery can reduce opioid consumption, decrease pain scores, lower the rate of nausea and vomiting, and improve patient satisfaction (1094).

Interestingly, Deng et al. have studied the effects of various intravenous anaesthetics on colorectal cancer progression. Their results show that propofol inhibits migration of colorectal cancer cells in vitro, but not in vivo. Etomidate promoted the migration of cancer cells both in vitro and in vivo. Furthermore, etomidate was shown to induce epithelial-mesenchymal transition (87-89). On the other hand, dexmedetomidine alone, or in combination with propofol or etomidate, had minor effects on the migration of colorectal cancer cells (1095).

In turn, Kahokehr and colleagues have performed a double blinded, randomized and placebo controlled trial in which the effects of intraoperative instillation and postoperative infusion of intraperitoneal local anaesthetic (IPLA) on recovery parameters after colectomy have been investigated. The study group, IPLA, received instillation of intraperitoneal ropivacaine (75 mg) before dissection and postoperative infusion of 0.2% solution at 4 ml/hr for 3 days continuously. The placebo group was treated as above with 0.9% saline solution. All patients were cared for in the setting of an established enhanced recovery after surgery (ERAS) program. Epidural infusion was stopped on day 2. Patients were discharged from day 3 onwards once criteria met. Perioperative data, recovery scores, complications and length of stay were recorded. Patients were followed up for 60 days. Results showed an improved early surgical recovery with a blunting of postsurgical systemic cytokines and cortisol. Furthermore, there was a significantly reduced pain and opioid use over and above the effect of an epidural infusion. There were no local anaesthetic related events. The complication rate, including anastomotic leakage, was equivalent between groups (1096).

Oh’s group has prospectively investigated the analgesic efficacy of ropivacaine wound infusion after laparoscopic colorectal surgery. Their results show that ropivacaine wound

infusion significantly reduces postoperative opioid requirements and the rate of nausea and vomiting (1097).

Campana et al. report that right laparoscopic colectomy for colon cancer is associated with a shorter operative time, an increased risk of ileus, and a longer hospital stay than left laparoscopic colectomy in high-volume centers (1098).

Cui and co-workers report that oxycodone and morphine both have inhibitory effects on immune function in patients undergoing radical resection of rectal cancer after surgery. However, oxycodone hydrochloride has a less pronounced effect compared to morphine hydrochloride (1099). In the morphine group the numbers of T lymphocytes and NK-cells were significantly lower at all studied time points compared with the oxocodone group. In other words and as far as the inflammatory stress response is concerned, one might advocate the use of oxycodone instead of morphine for postoperative pain treatment in patients undergoing rectal cancer surgery.

Finally, Maggiori and colleagues have investigated whether the combination of laparoscopic approach and full fast-track multimodal management can decrease postoperative morbidity following colorectal cancer surgery. In their multicentre, randomized, and controlled trial, laparoscopic surgery in combination with a full fast-track multimodal management had no beneficial effects on morbidity when compared to a limited fast-track program. Strikingly, only early intravenous catheter removal and the absence of intraoperative intravenous lidocaine infusion were identified as independent predictive factors of reduced postoperative morbidity following colorectal cancer surgery (1100).

5 Urogenital malignancies

5.1 Bladder / Renal cancer

Only one study could be identified dealing with renal cancer in relation to anaesthesia. Based on an in vitro study, Benzonana et al. report that the volatile anaesthetic isoflurane facilitates renal cancer growth by enhancing the malignant and metastatic potential of renal cancer cells (1101).

Interestingly, Kim's group reports that sevoflurane, as a maintenance agent of general anaesthesia, reduces the incidence of catheter-related bladder discomfort (CRBD) in patients undergoing transurethral excision of a bladder tumour when compared with desflurane (1102).

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 analysed. Results revealed a significantly higher mean time to recurrence in patients who had received an obturator nerve block (1103).

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 (1104).

Karadeniz cum suis have prospectively compared the effects of combined general and epidural anaesthesia with general anaesthesia and patient-controlled intravenous opioid analgesia on serum cytokine levels in patients undergoing radical cystectomy. Altough they were unable to demonstrate any significant differences in cytokine levels, the authors conclude that the combined general anaesthesia and patient-controlled epidural analgesia technique appears to be superior to the general anaesthesia and intravenous PCA because of lower intraoperative narcotic analgesic consumption ans shorter hospital stay (1105).

Weingarten and colleagues have retrospectively studied the effects of spinal analgesia on oncological outcomes in patients undergoing radical cystectomy for blader cancer. Their results show that systemic opioid use was reduced when general anaesthesia was combined with spinal analgesia in comparison to general anaesthesia alone. However, this opioid-sparing effect was not associated with improved oncological outcomes. Blood transfusion, on the other hand, was associated with increased mortality (1106).

Jang and co-workers also have studied the effects of type of anaesthesia on survival and cancer recurrence in patients after transurethral resection (TUR) of bladder cancer. In this retrospective study, regional analgesia (spinal or epidural) showed a higher 5-year survival compared with general anaesthesia through partial correlation analysis. However, this association proved not significant in the chi-square test and logistic regression analysis (1107).
It remains questionable, though, whether spinal and epidural analgesia can be placed into one group given their different mode and duration of action.

Based on the reults of their population-based study, Christopher Doiron and colleagues report to be unable to demonstrate any effect of epidural use on either short- or long-term outcomes in patients undergoing radical cystectomy for bladder cancer (1108).

Ahiskalioglu and co-workers have prospectively investigated the effects of epidural analgesia on pain management and stress response in patients undergoing percutaneous nephrolithotomy. In this randomized study, patients allocated to the epidural group reported significantly lower pain scores at all measurement times compared with those allocated to the general anaesthesia with postoperative intravenous PCA group. Furthermore, intraoperative blood loss and the level of stress response were lower in the epidural group. In other words, epidural analgesia, consisting of levobupivacaine and fentanyl, resulted in a intraoperative and postoperative suppression of the surgical stress response with reduced pain scores in the postoperative period (1109).

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 (1110).
Kaminska and co-workers endorse the importance of prostaglandin E2 in renal cell cancer development (1111).

Tabriz et al. demonstrate that COX-2 expression correlates with the histological subtype of renal cell carcinoma. Furthermore, possible links are also reported between COX-2 expression and pathologic state, nuclear grade and nodal involvement. No correlation was found between COX-2 expression and patient age, gender, tumour size, metastasis or survival (1112).

By contrast and based on the results of their population-based study, Nayan and co-workers report that increasing cumulative use of NSAIDs, angiotensin-converting enzyme inhibitors, and serotonine reuptake inhibitors was associated with markedly improved cancer-specific

survival. Furthermore, increasing use of NSAIDs was associated with markedly improved overall survival (1113).

Liu's group claims that metformin inhibits bladder cancer progression by inhibiting stem cell repopulation through the COX-2/PGE2/STAT3 axis. In other words, metformin exerts anticancer effects by inhibiting COX-2 and subsequently prostaglandin E2 (1114).

Mano and colleagues report that the NLR is an independent predictor of disease progression and recurrence in patients with non-muscle-invasive bladder cancer. 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 (150).

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 (1115).

Ozcan et al. have performed a retrospective study in which the prognostic significance of leucocytosis and NLR in patients undergoing radical cystectomy for bladder cancer was studied. Their results indicate that preoperative leucocytosis and NLR are independent prognostic factors for disease-specific survival in bladder cancer patients undergoing radical cystectomy (1116).

Bhindi and colleagues confirm the prognostic significance of NLR in patients with bladder cancer undergoing radical cystectomy. Based on the results of their study, NLR was reported as best complete blood count-based biomarker for predicting recurrence-free

survival, whereas NLR and haemoglobin were most efficient for predicting cancer-specific survival and overall survival (1117).

Based on the results of their retrospective study, Kang and co-workers claim that early postoperative NLR is a valuable predictor of outcome in patients with bladder cancer undergoing radical cystectomy and pelvic lymph node dissection. A high NLR (≥ 2.0) in the early recovery period was clearly associated with worse cancer-specific survival and overall survival. Additionally, patients with both pre- and postoperative elevated NLR (≥ 2.1 → ≥ 2.0) had worse oncologic outcomes than other groups of NLR changes (1118).

Favilla's group has performed a single-institutional longitudinal study in which NLR was investigated as a biomarker in patients with primary non-muscle invasive bladder cancer. Results showed that NLR ≥ 3.0 was associated with worse disease recurrence and shorter 5-year recurrence free survival. However, no association was found regardings disease progression and 5-year progression free survival. In other words, NLR predicted disease recurrence but not disease progression in non-muscle invasive bladder cancer (1119).

Cimen and colleagues state that pre-treatment measurement of NLR may provide valuable information for the clinical management of patients with non invasive bladder cancer. In their retrospective study, high NLR and low lymphocyte count were significantly associated with T1 stage, whereas low lymphocyte count was able to predict lamina propria invasion in these patients (1120).
Kang's group confirms the predictive value of NLR in patients with muscle-invasive bladder cancer undergoing radical cystectomy (1121).

Vliers et al. confirm the prognostic value of NLR in patients with localized clear cell renal carcinoma undergoing nephrectomy. In their study, a NLR ≥ 4.0 was significantly associated with worse 5-year cancer-specific and overall survival. The median follow-up was 9.3 years (158).

Kaynar concludes that NLR can be used to determine tumour invasiveness as a cost-effective, common and simple biomarker in bladder cancer (1122).

Ozyalvacli and colleagues confirm this finding. In their retrospective study, a NLR ≥ 2.43 was an independent predictor of recurrence in patients with high-grade pT1 non-muscle-invasive bladder cancer (1123).

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 (1124).
Ku and colleagues support this conclusion (1125).

Ohtake's group reports that pretreatment NLR may predict responses to gemcitabine and nedaplatin-based chemotherapy in advanced bladder cancer patients and/or their prognosis. The used cut-off point in this study was 4.14 (1126).

Morizawa and colleagues also report that NLR is a strong predictor of prognosis in patients with muscle-invasive bladder cancer undergoing radical cystectomy. Furthermore, postoperative chronological analysis revealed that the NLR in patients without bladder cancer recurrence remained low during follow-up, whereas the NLR in patients with cancer recurrence increased significantly in the last visit before recurrence was detected radiographically. The authors therefore conclude that these results suggest that an increase in the NLR during follow-up after radical cystectomy is a potential marker for the early detection of recurrence (1127).

De Giorgi cum suis 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 (1128-1130).

Huang and co-workers endorse the importance of NLR (and absolute neutrophil count) in predicting recurrence in patients with localized papillary renal cell carcinoma. The results of

their retrospective study revealed that an increased preoperative NLR (≥ 3.6) was significantly associated with recurrence-free survival (1131).

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 (1132).

Zhang et al. confirm the prognostic value of pre-treatment NLR in patients with metastatic renal cell carcinoma receiving targeted therapy. In their study, high NLR was an independent predictor of both overall survival and progression-free survival (1133).

Seah and co-workers retrospectively investigated patients with muscle-invasive bladder cancer (MIBC) treated with cisplatin-based neoadjuvent chemotherapy (NC) and radical cystectomy (RC). They report that patients responding to therapy exhibited a sustained decrease in NLR during NC and RC, whilst nonresponders exhibited a transient decrease in NLR, which then increased to above its baseline before radical cystectomy. Since the pattern of change in NLR during neoadjuvant chemotherapy varied significantly between responders and nonresponders, the authors hypothesize that a sustained decrease in inflammatory burden during neoadjuvant chemotherapy is associated with response (1134).

Kang’s group supports the predictive value of NLR in patients with non-invasive bladder cancer undergoing transurethral resection of the bladder tumour. In their retrospective study involving over 1500 patients, elevated NLR (≥ 2.0) was identified as a key predictor of overall survival (1135).

Ma et al. report that preoperative NLR and fibrinogen levels in patients distinguish between muscle-invasive bladder cancer and non-muscle-invasive bladder cancer with a sensitivity of 86% and a specificity of 42% (1136).

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 (1137).

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 (1138).

Marchioni's group has performed a systematic review and meta-analysis in which the prognostic significance of NLR in patients with upper tract urothelial cancer was investigated. Results show that NLR may have an independent role as a prognostic factor in patients with upper tract urotheial cancer undergoing surgical treatment (1139).

In patients with upper tract urothelial carcinoma that underwent radical nephro-ureterectomy NLR was associated with cancer-specific and overall survival (1140), and disease recurrence and cancer-specific mortality (1141). 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 pre-treatment NLR as a prognostic factor in metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. The results of their retrospective analysis demonstrate that only pre-treatment NLR, apart from calcium levels, was significantly associated with progression free survival. Median progression free survival was significantly lower in patients with a post treatment NLR > 2.0 compared with patients with a post treatment NLR of ≤ 2.0 (1142).

Chrom et al. even conclude that the incorporation of NLR and PLR in place of the neutrophil count and platelet count improves prognostic accuracy of the International Metastatic Renal Cell Carcinoma Database Consortium model (IMDC) (1143).

Auvray's group supports the predictive value of NLR in patients with metastatic urothelial carcinoma treated with first-line (platinum-based) chemotherapy (1144).

Hu and co-workers have performed a meta-analysis in which the prognostic role of NLR in patients with renal cell carcinoma was studied. Their results show that elevated NLR indicates a poorer prognosis for patients with renal cell carcinoma, and they conclude that NLR should be monitored in patients with renal cell carcinoma for rational risk stratification and treatment individualisation (1145).

Templeton and colleagues have investigated the prognostic value of NLR in patients treated for metastatic renal cell carcinoma. Based on the results of their retrospective analysis of 1199 patients from the International Metastatic Renal Cell Carcinoma Database Consortium and 4350 patients from 12 prospective randomized trials, the authors conclude that, compared with no change, early decline of NLR is associated with favourable outcomes, whereas an increase in NLR is associated with worse outcomes (1146).

Byun et al. conducted a multicentre cohort analysis in which the prognostic significance of NLR in non-metastatic renal cell carcinoma patients undergoing surgery was investigated. Based on the results, they conclude that higher NLR is associated with worse clinical behaviour of non-metastatic renal cell carcinoma. Also, NLR appears to be a significant prognostic factor for both recurrence-free survival and cancer-specific survival (1147).

Kuzman's group supports the prognostic value of NLR in patients with renal cell carcinoma treated with immunotherapy with high-dose interleukin-2 (1148).

Dalpiaz et al. have investigated the prognostic value of the pretreatment-derived NLR (dNLR) and original NLR in relation to the commonly used inflammation marker C-reactive protein (CRP) in a cohort of patients with clear cell renal carcinoma undergoing surgery. Results show that dNLR was an independent predictor of cancer-specific survival and metastasis-free survival, whereas CRP was confirmed as independent predictor of overall survival, cancer-specific survival, and metastasis-free survival.

Therefore, the authors conclude that in this cohort an elevated pretreatment CRP (≥ 10.0) and elevated dNLR (> 2.0) were robust independent predictors of cancer-specific survival and metastasis-free survival. In addition, their data suggest that CRP might be superior to both NLR and dNLR (1149).

By contrast, Yilmaz et al. report that NLR is superior to C-reactive protein (CRP) and white blood cell count (WBC) for predicting the development of acute kidney injury (AKI) in patients with severe sepsis. In this retrospective study, 118 consecutive 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 (1150).

Ishihara's group reports that systemic inflammation is associated with survival after second-line molecular-targeted therapy. In particular, CRP is reported to be a strong predictive biomarker of prognosis in patients with metastatic renal cell carcinoma (1151).

Finally, Boissier and colleagues have recently performed a review analysis in which the prognostic value of the NLR in renal oncology was investigated. Their results show that for localized renal cell carcinoma, a NLR < 3.0 was predictive of a reduced risk of recurrence. The prognostic value of NLR was stronger for metastatic or locally advanced renal cell carcinoma. A NLR < 3.0 predicted increased overall survival, progression free survival, and a response to systemic treatment. Therefore, the authors conclude that in current practice, NLR is a simple and inexpensive prognostic tool with potential improvement in the prognostic performance of normograms used in renal oncology (1152).

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 (1153).

Baik et al. have conducted a prospective, randomized, controlled and observer-blinded study in which the effects of an additional preoperative single thoracic paravertebral block (TPVB) to intravenous patient-controlled analgesia was studied in patients undergoing nephrectomy. Results showed that a single ultrasound-guided PVTB improved analgesia by reducing pains score and opioid consumption in patients undergoing nephrectomy (1154).

Copik and co-workers support the finding that TPVB reduces opioid consumption and pain intensity, and therefore is an effective part of a multimodal analgesia regimen in patients undergoing renal surgery. In their randomized and controlled trial, patients in the TPVB group required 39% less intravenous opioids over the first 48 hours, and had experienced less pain at rest throughout the first 24 hours. Furthermore, these patients also experienced fewer opioid-related adverse events and were less sedated during the first 12 postoperative hours (1155).

Interestingly, Karami and colleagues claim that acetaminophen may increase the risk of developing renal cel carcinoma. This claim is based on the results of their case-control, cohort and meta-analytic study (1156).

Interestingly, Jin’s group claims that postoperative pain is not significantly different between patients who undergo robot-assisted partial nephrectomy and patients who undergo

laparoscopic partial nephrectomy. Also, the incidence of opioid-related complications and duration of hospital stay were not significantly different between the two groups (1157).

Based on the results of their prospective, randomized, controlled trial, Khajavi and colleagues report that the combined subcutaneous infiltration of ketamine (0.5 mg/kg) and tramadol (0.5 mg/kg) at the incision site after renal surgery produces better analgesia and an opioid sparing effect during the first 24 hours when compared with placebo and infiltration with only ketamine or tramadol (1158).

Parker and co-workers have retrospectively evaluated the association between beta-blocker use and survival among surgically managed hypertensieve patients with clear-cell renal cell carcinoma. Their results show that beta-blocker use for hypertension within 90 days prior to surgery was not associated with the risk of progression, death from renal cell carcinoma, or death from any cause (1159).

Siemens et al. report that perioperative allogeneic blood transfusions are associated with substantially worse early outcomes and long-term survival in patients undergoing radical cystectomy for renal cancer (1160).

Liang’s group demonstrates that the administration of dexmedetomidine protects against cisplatin-induced acute kidney injury in mice through the regulation of apoptosis and inflammation (1161).

Finally, Kovac and colleagues have conducted a retrospective chart review in which the effects of additional epidural analgesia on survival following renal cancer surgery were investigated. Their results show that epidural analgesia at the time of surgical excision of localized renal cell carcinoma does not significantly impact cancer-specific survival. Nonetheless, epidural analgesia was associated with significantly improved overall survival (1162).

5.2 Prostate/ Testicular/ Penile 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.

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 (1163,1164).
Lee and colleagues have performed a meta-analysis in which the effects of neuraxial analgesia on recurrence and mortality after prostatectomy were investigated. They report that the anaesthetic technique used during oncologic prostatectomy is not associated with longer biochemical recurrence-free survival. By contrast, the use of neuraxial analgesia appeared to improve overall survival (1165).

Hong et al. have conducted a randomized, double-blinded study, in which the effects of epidural ropivacaine and sufentanil on the perioperative stress response after radical retropubic prostatectomy were studied. Based on the results, the authors state that epidural ropivacaine blunts the postoperative stress response in elderly patients undergoing radical retropubic prostatectomy. Cortisol levels increased significantly in the control group (patients receiving saline epidurally), as did the concentrations of epinephrine and norepinephrine, compared to the ropivacaine group. Furthermore, pain scores and analgesic requirement were lower in the ropivacaine group (1166).

As mentioned previously in the case of oesophageal cancer, Han and et al. claim that the use of propofol and/or dexmedetomidine as an induction agent in patients undergoing radical prostatectomy results in less oxidative stress compared to the use of midazolam. In their prospective and randomized trial oxidative stress indicators were assessed prior to and at 2 and 24 hours after oesophageal cancer surgery and radical prostatectomy. The patient group in which midazolam was used for induction of anaesthesia showed significantly higher oxidative stress compared with the propofol and dexmedetomidine group (621).

Lei and colleagues have performed a meta-analysis on the effects of combined general-epidural anaesthesia compared with general anaesthesia alone on survival and cancer recurrence. Although heterogeneous data were used for analysis, results showed that epidural-general analgesia might be associated with improvement of prognosis in patients with operable prostate cancer. No obvious relationship between improvement in prognosis of colorectal cancer and combined epidural-general anaesthesia was detected (1167).

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 (1168).
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 (1169).
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 (1170,1171). The same holds true for the adjunctive use of spinal anaesthesia on outcome in two other studies (1172,1173).

Interestingly, Maquoi et al. have performed a prospective, randomized study in which the analgesic effects of TAP blockade and intravenous lignocaine were analyzed following open prostate surgery. Their results reveal that additional TAP blockade and intravenous lignocaine do not improve postoperative analgesia after open prostatectomy, when compared to placebo (1174).

Despite these inconsistencies, Corsia and colleagues point out the importance of regional anaesthesia, avoiding pain and stress and reducing opioid consumption (1175).

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 (137).
Doat and co-workers endorse this hypothesis. In their population-based case-control study, men using NDAIDs had a decreased risk of prostate cancer, particularily men using preferential anti-COX-2 activity NSAIDs. The protective effect of NSAIDs appeared more pronounced in aggressive prostate cancer and in men with a personal history of prostatitis (1176). TOT HIER

This theory is further 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 (166).

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 chemo protective effects of anti-inflammatory drugs on prostate cancer (1177-1179). 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 (1179).

Veitonmäki et al. have studied the effect of NSAIDs use on prostate cancer survival in the Finnish prostate cancer screening trial. Results revealed that both pre- and postdiagnostic NSAID use was associated with an increased risk of prostate cancer. There was an increasing risk trend by cumulative dose and intensity of NSAID use. However, when the last three years were excluded from the analysis, the death risk diminished to a protective level. The authors conclude that the survival decrease among NSAID users is likely explained by symptomatic treatment of metastatic pain in patients with advanced prostate cancer. Otherwise, a preventive action of NSAIDs could be observed. Aspirine use was not significanty associated with prostate cancer survival (1180).

By contrast, Skriver's group reports that long-term, consistent low-dose aspirin use may provide modest protection against prostate cancer. However, non-aspirin NSAID use was associated with a slightly increased risk for prostate cancer (1181).

Interestingly, Kang et al. report similar findings. In their population-based cohort study, NSAIDs use was significantly associated with increased risk of prostate cancer, whilst aspirin and statin use were associated with elevated risk of kidney cancer (1182).

Based on the results of their cohort study, Templeton cum suis conclude that NLR can be used as a good prognostic score for metastatic castration-resistant prostate cancer (159). 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 (1183).

Minardi and colleagues report that a NLR ≥ 3.0 is associated with significantly higher incidence of prostate cancer recurrence. Furthermore, the authors also report that NLR was the most important factor able to predict recurrence in multivariate analysis, including age, total PSA and NLR (1184).
Özsoy and co-workers claim that a high preoperative NLR (≥ 3.0) is associated with aggressive prostate cancer and might be used to predict upgrading at radical prostatectomy (1185).

Gokce et al. state that NLR is a cost-effective and easily accessible tool that can be used in the decision-making process for treatment of low-risk prostate cancer cases (1186).
Finally, Tanik even claims that NLR is able to predict benign prostate hyperplasia (1187).

Maeda’s group, on the other hand, was unable to detect any association between NLR and biochemical failure after radical prostatectomy (1188).

Flamiatos et al. demonstrate that celecoxib has no effect on apoptosis, prostaglandins or androgen receptor levels in cancerous or benign prostate tissues (1189).

As mentioned previously, Huang and co-workers report that strong evidence exists that isoflurane, in contrast to propofol, should not be used in prostate cancer surgery. 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 chemo resistance. Exposure to propofol, on the other hand, resulted in partial reduction of cancer cell malignant activities (45).

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 (1190).
Kasuga and colleagues support the idea that pretreatment NLR may function as a biomarker to predict the prognosis in patients with penile cancer. A pretreatment NLR ≥ 2.8 was significantly associated with poorer cancer-specific survival (1191).

Lorente et al. report similar findings. In their study, focussing on patients with metastatic castration-resistant prostate cancer, pre-treatment NLR was associated with overall survival and response to treatment with second-line chemotherapy. Furthermore, this association was independent of pre-treatment 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 (1192).
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 (1193).
Finally, Uemura and colleagues report that a high NLR (≥ 3.83) is associated with worse overall survival in patients with castration-resistant prostate cancer treated with Cabazitaxel chemotherapy (1194).

Kawahara and Huang et al. support the importance of NLR in predicting prostatic carcinoma in men undergoing needle biopsy of the prostate (1195,1196).

Based on the results their retrospective trial, Lee and colleagues report that high NLR is significantly related to unfavourable clinicopathological outcomes and worse biochemical recurrence in patients with localized prostate cancer after radical prostatectomy (1197). Luo et al. have performed a meta-analysis to investigate the association between the NLR and prognosis of urologic tumours. Their results show that all overall survival, cancer-specific survival, recurrence-free survival, progression-free survival, and metastatic-free survival were significantly different between patients with an elevated NLR and those with a low NLR in various urologic tumours. Patients with a high NLR were deemed to have a poor prognosis (1198).

Bahig cum suis highlight the importance of the neutrophil count as a marker of survival in patients with localized prostate cancer. Based on the results of their retrospective survery, they conclude that the neutrophil count is an independent prognostic marker for overall survival in patients with localized prostate cancer undergoing radiotherapy (1199).

Oh et al. even report that NLR may be a potentially useful clinical marker in the detection of prostate cancer (1200).

Gu et al. have performed a meta-analysis in which the significance of NLR in patients with prostate cancer was investigated. Their results reveal that NLR showed consistent prognostic value in metastatic castration-resistant prostate cancer patients and predicted poor progression-free survival and recurrence-free survival in Asians, but not in Caucasians (1201).

Yuksel and co-workers confirm the prognostic value of NLR (and the white blood cell count) in the diagnosis of testicular cancer (1202).

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 acetylsalicylic acid. The reported median follow-up was 39 months (1203).

Lu et al. have performed a meta-analysis including 16825 patients with prostate cancer. In this analysis the association between beta-blocker use and mortality of prostate cancer was also examined. Results revealed that beta-blocker use was significantly associated with reduced cancer-specific mortality. However, no association was observed with all-cause mortality (1204).

As mentioned previously in the case of head and neck cancers, Chang and co-workers state that propranolol might reduce the risk of head and neck, oesophagus, stomach, colon and prostate cancers (275).

Cardwell, on the other hand, was not able to detect any relation between beta-blocker use and improved survival in patients with prostate cancer. In this nested case-control analysis, patients dying from prostate cancer were compared with up to three controls alive at the time of their death, matched by age and year of diagnosis. There was little evidence of a reduction in the risk of cancer-specific death in post-diagnostic beta-blocker users compared with non-users (1205).

As mentioned previously, Numbere et al. were also unable to confirm any protective effect of β-blockade on prostate cancer risk. In their case-control study, adrenergic blocker use was not associated with a reduced risk of prostate, breast, bowel and/or lung cancer (387). The same applies to Kao and colleagues. In their population-based cohort study, anti-arrhythmic drug usage was not associated with prostate cancer risk. This included sodium channel blockers, potassium channel blockers, beta-blockers, calcium channel blockers, and digoxin (1206).

In fact, Krönig's group claims that diabetes and beta 1-adrenergic receptor blockage are significant risk factors for lymph node metastasis and positive surgical margins in prostate cancer. This claim is based on the results of their retrospective chart analysis (1207).
A satisfactory explanation for these findings can not readily be given.

Based on the results of their retrospective cohort study, Kaapu and colleagues report that digoxin or other antiarrhythmic drugs use is not associated with any clear decrease in prostate cancer risk. However, the authors conclude that digoxin might have a benefit in long-term use by reducing the risk of high-grade disease (1208).

Nevertheless, Zahalka and co-workers demonstrate that endothelial β-adrenergic receptor signalling, via adrenergic nerve-derived norepinephrine in the prostate stroma, plays a key role in the activation of an angiogenic switch that fuels exponential tumour growth (1209).

In their paper, Braadland et al. expand further on the role of β-adrenergic receptor signalling in prostate cancer (1210).

5.3 Ovarian carcinoma

In several epidemiological studies, a correlation is found between the use of NSAID's and a decreased probability of developing ovarian carcinoma (1211).

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 down regulation of the E2F1 protein (1212).

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 (1213). The transcription factor NF-kB is suggested to play a pivotal role in the regulation of the immune system. Hayden et al. expand further on the importance of NF-kappaB and the immune response (1214).

Wong et al. describe a negative feedback in which the critical soluble mediators of type-1 immune effector cells, IFNγ and TNFα, synergize in the induction of COX-2 and the subsequent hyperactivation of myeloid-derived suppressor cells within the tumour microenvironment of ovarian cancer patients. This myeloid-derived suppressor cells hyperactivation and the resultant overexpression of indoleamine 2,3-dioxygenase, inducible nitric oxide synthase, Interleukin-10, and additional COX-2 result in a strong feedback suppression of type-1 immune responses. This paradoxical immune suppression driven by type-1 immune cell activation was foud to to depend on the synergistic action of IFNγ and TNFα, and could not be reproduced by either of these factors alone. Particularly, these negative feedback limiting type-1 responses could be eliminated by COX-2 blockade, thus allowing amplification of type-1 immunity in the ovarian cancer tumour microenvironment (1215).

Based on the results of a nationwide case-control study, Baandrup reports that low-dose aspirin use is associated with a reduced risk of epithelial ovarian cancer. Furthermore, a strong inverse association was detected between prescription use of paracetamol and risk of epithelial ovarian cancer. The risk estimates decreased with increasing duration and

intensity of paracetamol use, reaching a more than 50% reduction for the longest duration (>10 years) and the highest doses. By contrast, an inverse association between use of non-aspirin NSAIDs and risk of epithelial ovarian cancer was not observed. Finally, there was no apparent association between statin use and epithelial ovarian cancer risk, although the analysis by histologic type suggested an inverse association with the risk of mucinous tumors (1216).

Peres et al. have performed a population-based case-control study in African Americans in which the effects of aspirin and /or NSAIDs use on ovarian cancer risk were investigated. Their results support previous evidence that any NSAID use is inversely associated with epithelial ovarian cancer risk (1217).

As mentioned previously, propofol has been show to effectively inhibit proliferation and to induce apoptosis in human epithelial ovarian cancer cells (24).

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 (1218).

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 (1219).
Based on the results of their retrospective study, Merk et al. conclude that dexamethasone administration is not associated with an increased risk of cancer recurrence in women having surgery for endometrial cancer (1220).

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 (404).

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 (1221).

Courtney-Brooks and co-workers state that the use of continuous epidural analgesia in patients undergoing surgery for gynaecologic oncology results in lower pain scores without affecting the length of hospital stay. However, patients with continuous epidural analgesia (CEI) did have a longer length of unrinary catheterization but not an increased rate of urinary tract infection. There was a higher rate of postoperative venous thromboembolic events and CEI users (1222). A remarkable finding since Hollmann et al. have shown that epidural analgesia prevents immediate postoperative hypercoagulability without affecting physiologic aggregation and coagulation processes (1030).

Moslemi et al. have performed a prospective, randomized study in which patient controlled epidural analgesia was compared with intravenous patient controlled analgesia for postoperative pain management in patients undergoing major gynaecologic oncologic surgery. Results showed that both analgesic techniques provide proper postoperative pain control without any significant complications. But, regarding the lower sedative and respiratory depressant effects of epidural analgesia, is seems that epidural analgesia is a safer technique for postoperative pain relief in patients undergoing major open surgery (1223).

Oh and colleagues conclude that patient-controlled epidural analgesia is more effective for postoperative pain management in the first 3 postoperative days compared with patient-controlled intravenous analgesia in patients with ovarian cancer undergoing cytoreductive surgery, without increasing morbidity (1224).

Han's group also concludes that combined general anaesthesia with epidural analgesia is more suitable than general anaesthesia alone for patients undergoing ovarian cancer surgery. This conclusion is based on the results of theire retrospective analysis in which the effects of additional epidural analgesia on cellular immune functioning and prognosis were investigated. Results showed that the levels of TNF-α and IL-2 recovered faster in the epidural group, after an initial decrease, compared with the general anaesthesia alone group. Also, at 72 hours post surgery, the 5-year survival rate significantly increased in the combined general anaesthesia and epidural analgesia group compared with the general anaesthesia alone group (1225).

With respect to pro-inflammatory cytokines, Sanguinete and colleagues demonstrate that increased levels of IL-6 and IL-8 are associated with factors of worse prognosis in ovarian cancer. In the case of IL-6, higher serum levels were associated with overall survival less than 60 months; in case of IL-8, higher serum levels were associated with higher NLR (≥ 4.0), higher PLR (≥ 200), altered values of CA125, and stage IIIC disease (1226).

The same group also reports that patients with ovarian malignancies have higher levels of IL-6, IL-8, and nitric oxide (NO) compared to patients with benign ovarian neoplasms. Once more, elevated intracystic cytokine levels, especially IL-6 and IL-8, were associated with worse prognosis in patients with ovarian cancer (1227).

Dong and co-workers studied the effects of epidural analgesia during ovarian surgery. The results of their prospective, randomized study 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 (1228).

Based on the results of their retrospective study, Lin et al report that general anaesthesia combined with epidural analgesia results in better 3- and 5-yr survival when compared to general anaesthesia combined with intravenous opioids (1229).

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 (1230).

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 with lower overall rate of ovarian cancer recurrence compared with sevoflurane (1231).

By contrast, Iwasaki and colleagues report that the volatile anaesthetics isoflurane, sevoflurane and desflurane enhance the metastasis related cellular signalling of ovarian cancer cells. In other words, at clincally relevant concentrations these volatile anaesthetics appear to have strong effects on cancer cell biology which in turn could enhance ovarian cancer metastatic potential (1232).

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 (1233).

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 (1234).

Based on the results of their prospective study, Xu's group reports that combined general/epidural anaesthesia can improve the quality and efficiency in laparoscopy for ovarian neoplasms, with the advantages of reduced anaesthetic dosage, satisfactory postoperative analgesia, maintained hemodynamic stability, excellent uterine relaxation, and reduced time of anaesthesia induction, surgery, recovery, and extubation (1235).

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 (1236).

Yoshida and colleagues have conducted a prospective, randomized, placebo-controlled study in which the analgesic efficacy of bilateral continuous block in patients undergoing laparotomy for gynaecologic cancer was investigated. Their results show that the addition of continuous TAP blocks to single-injection TAP blocks reduces pain and morphine consumption following laparotomy for gynaecological cancer. It is worth mentioning that the bilateral oblique subcostal TAP blocks were performed after surgery (1237).

Yoshiyama and co-workers claim that the posterior TAP block provides more effective analgesia in the first 24 hours than the lateral TAP block in patients undergoing laparoscopic gynaecologic surgery (1238).

Sousa's group demonstrates that magnesium sulfate displays analgesic properties following laparoscopic gynaecologic surgery. In their double-blinded, randomized controlled trial,

intravenous magnesium sulfate (20 mg/kg in bolus followed by a continuous infusion of 2 mg/kg/hr during surgery) improved postoperative pain control, acting as an opioid sparing adjuvant. The analgesic effect was comparable to ketorolac 30 mg administered intravenously in the beginning of surgery (1239).

Melnikov et al. have compared the analgesic effects of thoracic paravertebral blockade with TAP blockade in patients undergoing major gynaecological surgery. In this prospective, randomized, controlled study, patients scheduled for a midline vertical laparotomy received either a bilateral TAP block or a bilateral paravertebral block at the level of Th10. Both blockades were performed preoperatively as a single injection of bupivacaine. All patients received patient-controlled postoperative analgesia via a pump. Results revealed that both blockades were associated with a reduction in opioid consumption and pain scores up to 48 hours postoperatively compared with the control patients. Therefore, the authors conclude that both blockades can serve as effective adjuncts in patients undergoing major gynaecological surgery. Although thoracic paravertebral blockade appeared to be more effective than TAP blockade, the latter performed under ultrasound guidance seems to be a more controlled and safe alternative (1240). However, it has to be mentioned that the analgesic effect of both blockades is maximal in the first postoperative day (532,1055). In case longer analgesic effects and a more pronounced attenuation of the inflammatory stress response are required thoracic epidural analgesia appears to be the preferred blockade in our opinion.

Murouchi and colleagues have performed a prospective, randomized study in which the changes in ropivacaine concentration and analgesic effects following bilateral single-shot TAP blockade and bilateral rectus sheath blockade (RSB) were investigated in patients undergoing laparoscopic ovarian surgery. Results showed that peak arterial ropivacaine concentrations were comparable during TAP and RSB, but peaked earlier during TAPB. Furthermore, duration of analgesia was significantly longer for TAPB than RSB following injection of 15 ml of 0.5% ropivacaine per side (1241).

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 (1242). Fortunately, these tumour-enhancing properties proved fully reversible by beta-blockade.

Watkins and co-workers even claim that use of non-selective beta-blockers in patients with epithelial ovarian cancer is associated with longer overall survival. This claim is based on their multicentre review in which over 1400 patients with ovarian cancer were studied (1243).

Hefner and Csef state that the available evidence does not justify the use of beta-blockers in clinical practice at the present time. However, preclinical research findings are described as very impressive (1244).

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 (341).

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 (1245). Cho, Thavaramara, Yesilyurt, Wang and Badora-Rybicka corroborate the prognostic significance of NLR in patients with ovarian cancer (1246-1250).

Ashrafganjoei and co-workers also report that both NLR and PLR seem to be useful methods for the prediction of surgical outcomes in patients with epithelial ovarian cancer. The gained cut-off points were NLR > 3.0, and PLR > 192.3 (1251).

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 (1252).

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 (1253).

Bakacak and co-workers also support the predictive value of NLR and PLR in ovarian malignancies. Based on the results of their retrospective analysis, they conclude that NLR, PLR, and lymphocyte count in combination with age and CA-125 levels, may be helpful to preoperatively distinguish malignant from benign ovarian masses (1254).

Based on the results of their meta-analysis, Prodromidou et al. conclude that both NLR and PLR appear to be promising screening and prognostic factors of epithelial ovarian cancer. However, the actual diagnostic cut-off value remains undefined until now (1255).

Hu and colleagues also have investigated the predictive value of PLR in patients with resected high-grade serous ovarian carcinoma. Their resuts show that a high PLR (> 188.8) was significantly associated with higher death rate (two-fold) and shorter median overall survival. Furthermore, the risk of a CA-125 level of > 640 U/ml was significantly greater in the high PLR group. Therefore, the authors conclude that PLR has potential as a prognostic biomarker for predicting survival of patients with resected high-grade serous ovarian carcinoma (1256).

Feng’s group reports that a high NLR (≥ 3.24) is significantly associated with worse progression-free survival, but not overall survival in patients with high-grade serous ovarian cancer (1257).

Based on the results of their systematic review and meta-analysis, Yang and co-workers conclude that NLR is an important predictor of prognosis in epithelial ovarian cancer (1258).

Komura et al. support the predictive value of NLR in ovarian cancer patients. In their retrospective analysis, neutrophilia (neutrophil count > 8.000/µl) and elevated NLR (≥ 4.0) were significantly associated with shorter survival. Consequently, they conclude that pre-treatment neutrophilia and elevated NLR are independent poor prognostic factors in epithelial ovarian cancer patients. Of these two prognostic factors, elevated NLR proved superior to neutrophil count in predicting survival (1259).

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 (1260).

Interestingly, Zhang et al. have studied the prognostic significance of preoperative PLR and compared this ratio to other systemic inflammatory response markers in ovarian cancer patients. Their results show that preoperative PLR appears to be superior to other SIR markers (CA-125, NLR, fibrinogen, CRP, and albumin) as a predictor of survival in ovarian cancer patients (1261).

By contrast, Luo's group claims that elevated fibrinogen levels are more important for predicting survival than serum CA-125 levels, NLR, and PLR in patients with epithelial ovarian cancer, in particular, in advanced stage disease. This claim is based on the results of their cohort study and meta-analysis (1262).

However, Topcu and co-workers claim that NLR is an ineffective marker in predicting the malignant characteristics of a pelvic mass (1263).

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 (1264).

This possible mechanism is reflected in the study performed by Diaz and colleagues. In their institutional retrospective review of patients with epithelial ovarian cancer, who underwent cytoreductive surgery followed by platinum-based chemotherapy, beta-blocker use was associated with a 54% reduced chance of death compared with that of non-users (1265).

Al-Niaimi et al. have retrospectively investigated the impact of perioperative beta-blocker use on patient outcomes after primary cytoreductive surgery in ovarian carcinoma. Their results show that perioperative beta-blocker use is associated with longer overall survival in patients undergoing primary ovarian cytoreductive surgery (1266).

Desale's group reports that perioperative fluid excess is common in patients undergoing cytoreductive surgery for advanced epithelial ovarian cancer and is independently associated with surgical site infections (1267).

Finally, Cai and colleagues suggest that dexmedetomidine may act to enhance the immune function by inhibiting the p38MAPK/NF-kB signalling pathway in rats with ovarian cancer. (1268). Further study results in humans have to be awaited.

5.4 Cervical carcinoma

Only relatively 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 (1269).

Hong and Lim state that pre-emptive 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 (pre-emptive 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 pre-emptive 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 pre-emptive 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 pre-emptive group were also significantly lower than in the control group (1270).

Li and colleagues report similar findings. In their prospective cohort study, patients undergoing radical resection for cervical cancer were randomized to either combined general/epidural anaesthesia or general anaesthesia alone. In the group receiving

general/epidural anaesthesia NK cell activity was less suppressed, there were higher levels of antitumorigenic cytokines (IL-2 and IFN-γ), and lower levels of protumorigenic cytokines (IL-1β, IL-6, and IL-8) at 4 and 24 hours after skin incision. The authors therefore conclude that combined general/epidural anaesthesia seems to be helpful to maintain the body's perioperative immune function compared to general anaesthesia alone in cervical carcinoma patients undergoing readical resection (1271).

Raghvendra et al. have compared the effects of epidural analgesia on postoperative pain with TAP blockade in patients undergoing total abdominal hysterectomy. In this single centre, prospective and randomized study patients were randomized to either the epidural group (epidural block placement combined with general anaesthesia) or the TAP group (single shot TAP block combined with general anaesthesia). Results revealed that the total opioid consumption in 24 hours was greater in the TAP group as compared to the epidural group. Pain scores at rest and on coughing were higher in the TAP group as compared with the epidural group at 6, 8, 12 and 24 hours postoperatively. Therefore, the authors conclude that epidural analgesia provides a greater tramadol-sparing effect with superior analgesia postoperatively as compared with TAP block in patients up to 24 hours following abdominal hysterectomy (1272).

Iyer's group reports similar results. In their randomized trial, patients either received postoperative epidural anaesthesia (10 ml bupivacaine 0,125% as a bolus and 10 ml 8th hourly for 48 hours), or ultrasound-guided TAP block through intravenous cannulas placed bilaterally. Analgesia at rest was comparable between the two groups in the first 16 hours postoperatively. However, at 24 and 48 hours postoperatively, the epidural group had significantly better analgesia at rest. Furthermore, in this group of patients, there was a significantly higher number of patients with nil or mild pain on coughing at all times. Paracetamol consumption was comparable in both groups, but tramadol consumption was significantly higher in the TAP block group at the end of 48 hours.
Based on these results, the authors conclude that the quality of analgesia provided by the epidural catheter is superior to that provided by TAP catheters both at rest and on coughing with reduced opioid consumption (1273).

Based on the results of their prospective and randomized trial, Chen and co-workers conclude that multimodal pre-emptive analgesia (including epidural analgesia) could significantly lower pain score, inhibit stress response, and reduce inflammatory response in patients undergoing transabdominal hysterectomy (1274).

Amsbaugh et al. conclude that epidural analgesia provides safe and effective pain control for patients receiving interstitial brachytherapy for gynaecologic cancer. In their retrospective analysis, combined modality epidural analgesia (consisting of a mixture of local anaesthetic with either fentanyl or hydromorphone) improved pain control and lessened oral and intravenous opioid requirements without increased risk of adverse effects compared with epidural analgesia with local anaesthetic alone (1275).

Nigam's group reports that the addition of clonidine (75 µg) to epidural ropivacaine provides superior analgesia than the addition of fentanyl (75 µg) to epidural ropivacaine without much difference in side effect profile in lower abdominal surgeries (1276).

Based on the results of their prospective, randomized, controlled trial, Ghisi and colleagues conclude that TAP blockade does not reduce morphine consumption during the first 24 postoperative hours after elective total laparoscopic hysterectomy (1277).

Rana and co-workers demonstrate that magnesium sulphate (150 mg), as an adjunct to bupivacaine in ultrasound-guided TAP block, reduces postoperative pain scores, prolongs the duration of analgesia and decreases demands for rescue analgesics in patients undergoing total abdominal hysterectomy under subarachnoid block (1278).

Hiller's group reports that neuraxial analgesia/anaesthesia reduces lymphatic flow and thus might, in theory, protect against iatrogenic dissemination of cancer cells during surgery. The most likely mechanism for reduction of lymphatic flow is thought to be temporary sympathectomy caused by neuraxial anaesthesia (1279).

As mentioned previously, there is also growing evidence that surgery per se might increase cancer risk and promote cancer metastasis by activating beta-adrenergic signaling, and thus

suppressing cell-mediated immunity and promoting angiogenesis and metastasis. Long and co-workers demonstrate that by activating beta-adrenergic signalling, surgery does increase angiogenesis and accelerates growth of endometriotic lesions in a mouse model. Furthermore, this facilitory effect of surgery is completely abrogated by beta-blokkade (1280). Obviously, further studies are needed to determine to what extent surgery can promote cancer growth in humans.

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 (1281).

Meanwhile, Wang and co-workers claim that the intraoperative and systemic administration of lidocaine exerts a protective effect on cell-mediated immunity in patients undergoing radical hysterectomy (1282).

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 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 (1283).

Samimi and co-workers have compared intravenous lidocaine infusion with intraperitoneal lidocaine infusion with respect to postoperative analgesia in patients undergoing abdominal

hysterectomy. In this prospective, double blind and placebo controlled study patients (n=109) were randomly allocated to three groups: 1. The IV (intravenous) group: patients in this group received a bolus of 2% 1.5 mg/kg intravenous lidocaine 30 minutes before incision, followed by a continuous lidocaine infusion of 2 mg/kg, and before wound closure an intraperitoneal injection of normal saline; 2. The IP (intraperitoneal) group received normal saline intravenously and intraperitoneal lidocaine 3 mg/kg; 3. The P (placebo) group received normal saline both intravenously and intraperitoneally. Results revealed that pain scores were significantly lower in IP and IV groups compared with placebo. Furthermore, total morphine consumption and time to first request of rescue analgesic were also lower in the IP and IV groups. The incidence of vomiting was comparable between the three groups, but nausea was more frequently reported in the P group. IP and IV groups were not statistically different for all investigated variables. There were no notable lidocaine-related adverse effects. Therefore, the authors conclude that lidocaine administration, both intravenously and intraperitoneally, is effective in reducing postoperative pain and also has an opioid sparing effect in abdominal hysterectomy without any major adverse effects (1284).

Xu and colleagues demonstrate that intravenous lidocaine combined with dexmedetomidine infusion significantly improves postoperative pain and enhances recovery of bowel function following abdominal hysterectomy. In this prospective, randomized study, patients received either normal saline infusion, lidocaine infusion (1.5 mg/kg bolus, and 1.5 mg/kg/h continuous infusion), dexmedetomidine (0.5 µg/kg bolus and 0.4 µg/kg/h infusion, or lidocaine and dexmedetomidine infusion in the mentioned dosages (1285).

By contrast, Dewinter et al. report that intravenous lidocaine failed to improve postoperative pain and reduce opioid consumption in patients undergoing laparoscopic sterilization. Although they were no beneficial effects on pain and opioid consumption in this double-blind, randomized, placebo-controlled trial, intravenous lidocaine infusion did reduce time to discharge readiness in this group of patients. Remarkebly, patients in the placebo group suffered significantly less from nausea and required less postoperative nausea and vomiting rescue medication compared with the lidocaine group (1286).

Chung et al. have studied the ON-Q pain management system in elective gynaecologic cancer patients undergoing lower midline laparotomy (1287). 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 anaesthetic 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 supraperitoneal layer of the abdominal incision via the ON-Q pump. The other group received intravenous patient-controlled analgesia using fentanyl and ondansetron. Postoperative 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.

Lee and colleagues have studied the effects of additional continuous wound infiltration on postoperative pain management in patients undergoing surgery for gynaecologic cancer. Based on the results of their retrospective study, they conclude that combining a continuous wound infiltration system (ON-Q pain management system) with intravenous patient-controlled analgesia significantly lowers mean NRS scores during the first 48 postoperative hours (1288).

Turner et al. have investigated postoperative pain scores and opioid use in robotic-assisted versus traditional laparoscopic hysterectomy in patients undergoing hysterectomy for endometrial cancer. Their results indicate that a robotic-assisted approach was not associated with a reduced postoperative opioid or anti-emetic use compared to the traditional laparoscopic approach (1289).

As mentioned previously, Shoar et al. demonstrate that patients undergoing laparoscopic surgery with low-pressure pneumoperitoneum experience the same level of systemic stress

response compared to patients undergoing laparoscopy with standard-pressure pneumoperitoneum (905).

Although postoperative cell-mediated immune function is better preserved in patients after laparoscopic-assisted surgery than after open surgery, the inflation of the abdomen alone results in a significant stress response. In our opinion, one should therefore take the effects of pneumoperitoneum during laparoscopic surgery into account when deciding which anaesthetic technique should be used with resepct to the attenuation of the surgical stress response.

Based on the results of their retrospective cohort study, Rivard and colleagues claim that the administration of intraperitoneal bupivacaine is associated with improved postoperative pain control in patients undergoing minimally invasive gynaecologic cancer surgery. Patients who received intraperitoneal bupivacaine had lower median narcotic use on the day of surgery and the first postoperative day compared with those who did not receive intraperitoneal bupivacaine. Furthermore, median patient-reported pain scores were lower on the day of surgery in the intraperitoneal bupivacaine group (1290).

As mentioned previously in the case of thocacotomy (543), the use of liposomal bupivacaine in additional locoregional analgesic techniques also appears to be promising in the case of robotic assisted hysterectomy. Hutchins et al. have conducted a prospective randomized controlled observer-blinded study in which ultrasound-guided subcostal transversus abdominis plane (TAP) blocks with bupivacaine were compared with TAP blocks with liposomal bupivacaine in patienst undergoing robotic assisted hysterectomy. Results showed that total opioid use in the first 72 hours after injection was significantly decreased in the group that received liposomal bupivacaine compared to bupivacaine. Furthermore, patients in the liposomal bupivacaine group had significantly lower maximal pain scores at all time periods studied, as well as decreased incidence of nausea and vomiting (1291).

Kim and co-workers claim that the intravenous administration of a single-dose dexamethasone (10 mg 1 hour pre-intervention) as an adjunct to fentanyl-based intravenous

PCA is effective in reducing inflammation and pain during the first 24 hours after uterine artery embolization. Furthermore, the incidence of severe nausea and vomiting was significantly lower in the dexamethasone group (1292).

Brøns et al have investigated the effect of NSAID use on endometrial cancer risk. The results of their nationwide case-control study revealed no association between NSAID use and endometrial cancer risk overall. However, there were some indications of risk reductions associated with low-dose aspirin use among nulliparous women and with non-aspirin NSAID use among women having used hormone replacement therapy (1293).

Meanwhile, Verdoodt et al. report that (based on the results of their meta-analysis) regular use of aspirin or non-aspirin NSAIDs is associated with a marginally reduced risk of endometrial cancer. Larger risk reductions were linked wth high frequency of NSAID use and high body mass index (BMI > 30) (1294).

By contrast, Brasky and co-workers claim that the use of NSAIDs is associated with increased endometrial carcinoma-specific mortality, especially in patients with endometrioid type tumours (1295).

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 (160). 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 (1296).
Haruma and colleagues also state that pre-treatment NLR is a predictor of poor prognosis in patients with endometrial cancer. Unfortunately, in this study, the NLR cut off point was not mentioned (1297).

On the other hand and based on the resuts of their retrospective study, Cummings et al. report that a NLR ≥ 2.4 is a strong prognostic indicator for endometrial cancer. Furthermore, PLR (≥ 240) also proved to be an independent predictor of survival. Combining NLR with PLR scores stratified patients into low (NLR low and PLR low), intermediate (NLR high or PLR high) and high-risk (NLR high and PLR high) groups (1298).

Takahashi confirms that an elevated neutrophil or leucocyte count at the time of the initial diagnosis is an independent prognostic factor in patients with surgically treated endometrial cancer (1299).

Cakmak et al. have studied 110 patients with abnormal uterine bleeding. Peripheral blood was collected and both NLR and PLR were calculated before endometrial curettage was performed. Based on pathology results, patients were then divided into 3 groups: group 1, patients with endometrial hyperplasia (EH) without atypia; group 2, patients with EH and atypia; group 3, patients with neither hyperplasia, nor atypia as control group. Blood cell counts, NLRs and PLRs were compared among these groups. Results showed that leucocyte and neutrophil counts were higher in patients with endometrial hyperplasia and atypia compared with those in group 1 and group 3. Furthermore, NLR of patients with hyperplasia and atypia was significantly elevated when compared to groups 1 and 3. Therefore, the authors conclude that NLR can be used as a predictor of atypical endometrial hyperplasia in patients with abnormal uterine bleeding (1300).

Wang’s group has retrospectively investigated the predictive value of NLR, PLR and red cell distribution width (RDW) in patients with cervical cancer. They report that NLR and PLR values were higher in patients with cancer compared with controls, and these values were consistently elevated during tumour progression while the RDW was uninformative. Increased NLR was associated with lymph node metastasis and depth of stromal infiltration, and increased PLR correlated only with lymph node metastasis. The pretreatment NLR and PLR value was a significant predictor of lymph node metastasis, which enhanced when NLR and PLR values were combined. Furthermore, NLR and PLR were as effective as squamous cell carcinoma antigen (SCC-Ag) for predicting distant tumour metastasis.

However, no prognostic significance of NLR or PLR was found in patients with early cancer stages. Based on these results, they conclude that pretreatment NLR and PLR might be helpful to predict the presence of distant and lymph node metastasis in patients with cervical carcinoma, but do not represent adequate prognostic factors for early stage cervical cancer patients (1301).

Onar and colleagues report that pretreatment NLR and PLR are associated with large tumours, lymph node metastasis, and poorer therapeutic responses to definitive chemoradiotherapy in patients with cervical cancer. Furthermore, NLR and lymph node metastasis were found independently predictive of overall survival and progression-free survival (1302).

Based on the results of their meta-analysis, Huang's group concludes that elevated pretreatment NLR could serve as a predictive factor of poor prognosis for cervical cancer patients (1303).

As reported earlier in the case of colon cancer (1029), Seebacher and co-workers confirm the prognostic value of pre-treatment plasma fibrinogen levels in patients treated for endometrial cancer. In their retrospective 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 (1304).
Furthermore, Guzel and colleagues claim that pre-treatment NLR also can be used as a biomarker of invasion in gestational trophoblastic disease (1305).

Gungorduk et al. have studied the prognostic significance of NLR (and PLR) in primary fallopian tube carcinoma and conclude that preoperative NLR is a prognostic factor. In this multicentre 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 (1306).

Kim and co-workers report that anaesthetic techniques have an effect on NLR after laparoscopy-assisted vaginal hysterectomy. This claim is based on the results of their prospective, randomized study in which 40 patients scheduled for vaginal hysterectomy were included. Patients were divided into 2 groups: one group received total intravenous anaesthesia with propofol and remifentanil (PR-group), the other group received inhalational anaesthesia with sevoflurane (S-group). Differential counts of leukocytes with NLR were obtained just prior to induction (T1), at the end of surgery (T2), 2 hours after surgery (T3), and 24 hours after after surgery (T4).
There was a significant increase in total leukocytic count, neutrophil count and NLR, and a decrease in lymphocytic count at all time points after surgery in both groups. NLR was significantly lower in group PR compared with group S at T3. Furthermore, in group PR the increase in NLR at T2 and T3 was significantly lower compared with that in group S (1307).

As mentioned previously, Turner and colleagues have investigated the postoperative pain scores and narcotic use in robotic-assisted versus laparoscopic hysterectomy for endometrial cancer staging. In their retrospective analysis, a robotic-assisted approach was not associated with reduced PACU narcotic or anti-emetic use compared with the traditional laparoscopic approach. Twenty-four-hour narcotic and anti-emetic use was also not different between the 2 approaches (1289).

Merk et al. state that dexamethasone administration (as a prophylactic for postoperative nausea and vomiting) is not associated with an increased risk of recurrence in women having surgery for endometrial cancer (1220).

With respect to dexamethasone, Corcoran and co-workers have prospectively investigated the effects of intraoperative dexamethasone on immunity and inflammation in patients undergoing elective laparoscopic gynaecological surgery. Their results show that a single intravenous administration of 4 mg dexamethasone following induction of anaesthesia attenuates the inflammatoty reaction and alters immune cell counts at 24 hours postoperatively. There was no effect on white cell counts at 48 hours and 6 weeks postoperatively. The clinical importance of these findings remains yet unknown (1308).

Ke’s group reports that prostaglandin E2 promotes proliferation and invasion by enhancing SUMO-1 activity via EP4 receptor in endometrial cancer (1309).

Dickson and colleagues have performed a randomized, controlled trial in which the introduction of a formal enhanced recovery after surgery program (ERAS) was investigated on length of hospital stay following gynaecologic oncologic surgery. The protocol elements included: preoperative counseling, regional anaesthesia, intraoperative fluid restriction, and early postoperative ambulation and feeding. Results showed that when compared with usual care, the introcuction of a formal enhanced recovery after surgery protocol did not significantly reduce length of stay following laparotomy (1310).

As mentioned previously, Bashandy and Elkholy have studied the effects of an ultrasound-guided pre-emptive single-injection rectus sheath block on postoperative pain in patients undergoing abdominal cancer surgery with midline incision, and conclude 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 (1070).

Yassin and colleagues have prospectively compared the analgesic efficiency of ultrasound guided rectus sheath block (RSB) with thoracic epidural analgesia (TEA) following abdominal surgery with a midline incision. Based on the results of this randomized, controlled trial, they conclude that continuous TEA has better opioid sparing effects markedly during the early 72 hours postoperatively than that of intermittent RSB with catheters inserted under real-time ultrasound guidance. RSB could thus be used as an alternative when TEA can not be employed in patients undergoing laparotomies with an extended midline incision, especially after the first postoperative day (1311).

As mentioned previously in the case of mastectomy, thoracic surgery, and robotic assisted hysterectomy, the use of liposomal bupivacaine results in an opioid sparing effect and longerlasting analgesia (478,543,1291).

Seagle's group has performed a cost-effectiveness analysis between TAP block with liposomal bupivacaine and opioids for acute postoperative pain following laparoscopic hysterectomy for endometrial cancer. Based on the results, the authors conclude that TAP with liposomal bupivacaine is robustly cost-effective at conventional willingness-to-pay thresholds. Furthermore, TAP was cost-saving compared to opioids-only when the same-day discharge rate among TAP users was greater than among opioid-only users (1312).

Wang et al. have conducted a meta-analysis in which the effects of preoperative pregabalin administration on acute postoperative pain following hysterectomy were investigated. Results show that perioperative use of pregabalin reduces postoperative pain, total morphine consumption, and morphine-related complications following hysterectomy. However, different doses of pregabalin were used and the optimal dose still has to be determined (1313).

Finally, Sanni et al. report that, based on their UK population-based study, no significant associations were observed for post-diagnostic use of statins, β-blockers, or low-dose aspirin and endometrial cancer survival (1314).

5.5 We were unable to identify any study results focussing on vulvar carcinoma (recurrence) and its relation to anaesthesia.

6. Skin/ soft tissue, muscle and bone malignancies

Relatively few study results are available focussing on surgical oncology of skin, soft tissue, muscle, and bone 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 (1315,1316).

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 (1317).
Meng et a. support this finding. In their meta-analysis, epidural analgesia provided significantly superior analgesia, higher patient satisfaction, and decreased overall opioid consumption compared with intravenous pantient-controlled analgesia following major spine surgery (1318).

With respect to epidural analgesia, Bindra and colleagues state that ropivacaine and bupivacaine provide effective epidural analgesia for lower limb surgery. However, postoperative pain was less with 0.5% bupivacaine and 0.75% ropivacaine as compared to 0.5% ropivacaine (1319).

Van Waesberghe and co-workers have performed a systematic review and meta-analysis in which epidural anaesthesia was compared with general anaesthesia with respect to mortality in patients with a hip fracture. Results suggest that neuraxial anaesthesia is associated with a reduced in-hospital mortality and length of hospitalisation. However, there was no difference in 30-day mortality between the general anaesthesia and epidural analgesia groups (1320).
Smith et al. report similar findings. In their systematic review and meta-analysis, neuraxial anaesthesia, either combined with general anaesthesia or used alone, was not associated with with decreased 30-day mortality in patients undergoing major truncal and lower limb

surgery. However, neuraxial anaesthesia may improve pulmonary outcomes and reduce resource use when compared with general anaesthesia (1321).

Based on the results of their meta-analysis, Zorrilla-Vaca et al. claim that existing evidence supports the overall beneficial effects of neuraxial anaesthesia in decreasing the development of surgical site infections after joint arthroplasty (1322).

Szucs'group reports that a single dose of dexamethasone 0.1 mg/kg administered before operative fixation of fractured neck of femur significantly improves the early postoperative analgesia (1323).

Interestingly, a larger retrospective study on melanoma excision showed that the use of volatile anaesthetics as part of general anaesthesia was associated with worse survival when compared to the use of local anaesthetics (41).

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 (1324).

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 (1325).

Based on their meta-analysis, Zhang and co-workers were unable to find any statistically significant chemo protective effects of NSAID's on non-melanoma skin cancer (NMSC) (1326).

Muranushi and colleagues, on the other hand, have conducted a systematic review based on published epidemiological studies and investigated 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 (1327).
This same group has also performed a meta-analysis in which the effect of oral NSAIDs on basal cell carcinoma (BCC) was studied. Once again, their results indicate that the intake of NSAIDs may help prevent BCC, particularly in high-risk populations (1328).

Based on the results of their phase II, randomized controlled trial, Brinkhuizen and colleagues even report that topical diclofenac is a promising new treatment for superficial basal cell carcinoma. Patients who were treated with topical diclofenac showed a significant decrease in the levels of proliferation and anti-apoptosis compared with patients who were not treated with topical diclofenac (1329).

Reinau et al. report comparable results and conclude that patients predisposed to non-melanoma skin cancer might benefit from chemoprevention with NSAID's (1330).

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 (1331).

Al-Nimer et al. report that aspirin and diclofenac inhibit the growth of fibroblast and rhabdomyosarcoma cell by inhibiting the up-regulation of cyclooxygenases enzymes in cancer cells. Aspirin proved more effective than diclofenac against the growth of rhabdomyosarcoma cell line (1332).

Upadhyay and colleagues conclude that ibuprofen reduces proteasome activity, enhances the aggregation of ubiquitylated abnormal proteins, and also elevates the accumulation of crucial proteasome substrates. Ibuprofen treatment thus causes mitochondrial abnormalities and releases cytochrome C into cytosol (1333).

Panza et al. demonstrate that a positive COX-2 expression ≥ 10%, as opposite to a positive expression ≤ 9%, is associated with a significant reduction of progression-free survival of about 3 years in patients with metastatic melanoma. These findings suggest that COX-2 expression may become an useful diagnostic tool in defining melanoma malignancy as well as argue for a possible therapeutic use of NSAID as add on therapy in selected cases (1334).

As mentioned previously in the case of prostate and breast cancer, the absence of chemo protective 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 (137). 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 (1335,1336). 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 (1337).

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 ≥ 2.39 had a significantly decreased disease-free and overall survival (1338).

Jiang and co-workers have evaluated the association between possible risk factors and survival for metastatic soft tissue sarcoma. The results of their study indicate that both monocyte ratio and NLR are significant prognostic predictors of overall survival and progression-free survival. The authors therefore conclude that patients with a monocyte ratio or NLR > 1.0 should be screened out as candidates for more intensive or aggressive multimodality treatments and more aggressive follow-up (1339).
Broecker's group confirms that postoperative complications following resection of truncal and extremity soft tissue sarcoma are associated with decreased disease-free survival (1340).

Liu (T) et al. claim that low preoperative lymphocyte-to-monocyte ratio (LMR) is associated with a poor prognosis in patients suffering from osteosarcoma (1341).
Liu (B) and colleagues, on the other hand, state that NLR, Glasgow prognostic score, and occurrence of metatstase were top risk factors associated with death of osteosarcoma patients in their retrospective analysis (1342).

Xia and colleagues confirm the prognostic value of pretreatment NLR in patients with osteosarcoma. Pre-surgery NLR was an independent prognostic indicator for overall survival and progression-free survival (1343).

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 (185).

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 tumour microenvironment reactivity through β3-adrenoreceptors during melanoma progression (1344).

Based on the results of their literature search, Colucci and Moretti report that activation of β-adrenoreceptors by catecholamines, usually released under stress conditions, has been found to trigger pro-tumorigenic pathways contributing to cell proliferation and motility, immune system regulation, apoptosis, epithelial-mesenchymal transition, invasion and neoangiogenesis (1345).

Lemeshow and co-workers have performed a population-based cohort study in which the use of beta-blockers in patients with malignant melanoma was studied in relation to survival. Based on the results, the authors conclude that increased survival time of patients with melanoma receiving β-blockers suggests that this class of drugs may hold promise in treatment strategy for these patients (1346).

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 chemo preventive 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 (1347).

Zhou and colleagues demonstrate that propranolol may inhibit melanoma by activating the intrinsic apoptosis pathway and inactivating the MAPK and AKT pathways (1348).

However, as in the case of breast, colorectal and prostate cancer, Cardwell and co-workers were unable to detect any relation between post-diagnosis beta-blocker use and mortality in patients with malignant melanoma (582,983,1077,1205). In their population-based nested case-control study, beta-blocker medications were prescribed after malignant melanoma diagnosis to 20.2% of 242 patients who died from malignant melanoma and 20.3% of 886 matched controls. Consequently, the authors conclude that there was no association between post diagnosis beta-blocker use and melanoma-specific death (1349).

Interestingly, Wrobel and Le Gal have investigated the effect of non-cardioselective and cardioselective β-blockers on melanoma progression at the cellular, molecular and tumour levels. Their results show that the non-cardioselective β-blocker propranolol inhibits proliferation and induces apoptosis in primary cell cultures derived from a primary and a metastasis of human melanoma and in melanoma cell lines. By contrast, the cardioselective β-blocker metoprolol hardly affects melanoma cell survival or proliferation (1350). Apparently, with respect to tumour growth inhibition, β-2 adrenergic receptor blockage appears to be more important than β-1 adrenergic receptor blockage.

Based on the results of their prospective study, De Giorgi and colleagues report that β-blockers protect patients with thick cutaneous melanoma from disease recurrence (1351).

Wnorowski et al. confirm the importance of β-2 adrenergic receptors in the proliferation of melanoma cells. In their study, motility of human-derived melanoma cells was dose-dependently and time-dependently inhibited by the highly-selective β-2 adrenergic receptor agonist (R,R')-4'-methoxy-1-naphthylfenoterol (1352).

As mentioned previously, de Lorenzo and colleagues have demonstrated that sleep-deprivation (in mice) reduces both the number of NK cells and their cytotoxic activity against melanoma cells in vitro. Treatment with the non-cardioselective β-blocker propranolol reversed these effects, indicating that a significant role of β-adrenergic receptors on NK cell function. Furthermore, sleep deprivation also resulted in an increase in corticosterone levels and expression of β-2 adrenergic receptors in NK cells (14).

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 (1353).

Surprisingly, Tang et al. claim that current evidence from observational studies suggests that the use of diuretics or β-adrenergic blocking agents may be associated with an increased risk of malignant melanoma (1354).

Finally, Fitzgerald, in his paper, provides us with an epidemiological overview of the use of beta-blockers, the role of norepinephrine and carcinogenesis (1355).

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-blockers, and are also predisposed 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 stimulate 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.

Based on the results of their prospective randomized study, Chloropoulou et al. conclude that epidural anaesthesia followed by epidural analgesia produces less inflammatory stress response compared with spinal anesthesia followed by intravenous morphine analgesia in patients undergoing total knee arthroplasty (1356).

Horvathova's group has conducted a study in mice in which the effects of sympathectomy on melanoma characteristics were investigated. Their results show that sympathectomy induces complex changes in the tumour microenvironment reducing tumour weight and affecting expression of tumour-related genes in melanoma tissue, in other words reducing melanoma growth (1357). This finding might explain why epidural analgesia results in less severe inflammatory response and consequently better preservation of immune function in patients undergoing cancer surgery.

Velasquez and colleagues have investigated the immune response following surgery for malignant bone tumours. Their results show that both the number of NK-cells and their function decreases significantly after surgery. The maximal decrease in function occurred 5 days postoperatively. Furthermore, the serum concentrations of IL-6 were significantly increased on postoperative days 1, 3 and 5. By contrast, serum concentrations of IL-2 and IL-4 did not change postoperatively. In other words, a significant inflammatory response and innate immune suppression occurres after surgery for bone cancer (1358). Strikingly, the immune suppression is once more reported to last for several days.

Wei et al. demonstrate in their prospective and randomized trial that epidural anaesthesia combined with general anesthesia has a beneficial effect on the preservation and restoration of immune function in patients with osteosarcoma undergoing radical resection (1359).

Two other randomized studies support the conclusion that epidural analgesia combined with general anaesthesia suppresses the surgical stress response in patients undergoing hip and knee arthroplasty, and total hip replacement (1360,1361).

As mentioned previously, Joy and co-workers have shown that epidural ropivacaine with dexmedetonidine significantly reduced the total propofol dose required for induction of anaesthesia in patients undergoing lower extremity and abdominal surgery. Furthermore, this combination decreased the onset time of sensory and motor block and provides good haemodynamic stability (673).

Based on the results of their retrospective study, Janssen et al. report that allogeneic blood transfusion did not decrease survival in patients who underwent surgery for long-bone metastatic fractures (1362).

Haughom and co-workers claim that neuraxial anaesthesia is associated with fewer blood transfusions in patients undergoing total hip arthroplasty (1363).

Finally, Liu and colleagues have retrospectively investigated 16.555 patients following knee arthroplasty. Patients who had received spinal or epidural anaesthesia had a significantly lower infection risk within 30 days of surgery compared with patients who had received general anaesthesia (1364).

7. Neuroendocrine malignancies

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

However, Derikx et al. report that colonic neuroendocrine tumours are more prevalent in patients with inflammatory bowel disease compared to the general population (1365).

Pan and colleagues have performed a randomized, controlled study in which the effects of epidural preemtive analgesia on stress reaction were investigated in patients undergoing retroperitoneal laparoscopic adrenalectomy. Their results show that compared with general anaesthesia, general anaesthesia combined with epidural analgesia alleviates the stress response in patients undergoing laparoscopic adrenalectomy (1366).

Finally, Salman et al. report that NLR and PLR are simple laboratory findings that can be used to identify neuroendocrine tumours with a worse outcome (1367).

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 (1368).

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 (1369).

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 (1370).

Schneider and colleagues have studied the effects of RFA-mediated necrosis on the immune responses in 12 non-small cell lung cancer patients undergoing RFA. In patients developing local or lymphogenic tumour relapse (n=4) there was an early significant increase in the concentration of tumour necrosis factor (TNF)-α. This change was associated with an elevated activity of circulating myeloid-derived suppressor cells indicated by an increased nitric oxide production in these cells. According to the authors, this might be an early indicator of the incomplete RFA and subsequently a potential tumour relapse in non-small cell lung cancer (1371).

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 (1372).

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 (1373).

Tohme and colleagues performed a retrospective study in patients with unresectable colorectal cancer undergoing hepatic radio embolization, 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 radio embolization for metastatic colorectal cancer (1374).

As mentioned previously, D'Emic and co-workers confirm that both pre- and/or post-treatment NLR and/or PLR are predictive of clinical outcome in patints undergoing selective internal radiation. Furthermore, they report that the largest increase in risk of death as well as local and extrahepatic disease progression was related to change in PLR (806).

Dubut et al. state that CT-guided paravertebral blockade for microwave ablation of kidney tumours is a promising new technique and may be used as an alternative to general anaesthesia or conscious sedation (1375).

9. Transarterial chemoembolization 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, nor pain, nausea, and 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 two papers focussing on this issue (1376,1377). The first paper underlines the complaints following this procedure as described above, and several recommendations are provided. The second paper demonstrates that the perioperative administration of parecoxib significantly improves postoperative pain control following TACE.

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 (1378).

Huang et al. confirm that a high pretreatment NLR (> 3.3) is associated with worse survival in patients with unresectable hepatocellular cancer undergoing transarterial chemoembolization. However, increased NLR after transarterial chemoembolization was associated with a better outcome (1379).

Zhou and colleagues support the prognostic value of NLR in patients with hepatocellular carcinoma following transarterial chemoembolization. NLR > 2.6 following TACE was significantly associayed with shorter overall survival (1380).

Kim et al. report that transarterial radioembolization (TARE) is an emerging intra-arterial brachytherapy characterized by potent anti-cancer effect given by radiation but minimal embolic effect (1381). Until now, no studies have been published focussing on TARE in relation to anaesthesia, anaesthetic techniques and/or recurrence of cancer.

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 (1382,1383).

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 (1384).
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 still is 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 (1385).

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/loco regional anaesthesia. However, they caution that these findings must be interpreted cautiously (1386).

Based on the results of their systematic review, Soltanizadeh et al. state that currently four propensity-adjusted retrospective studies suggest that total intravenous anaesthesia might be

the preferred anaesthetic choice in cancer surgery instead of inhalational anaesthesia. However, evidence is of low quality and randomized clinical trials are required (1387).

In their paper, Das and colleagues indorse that perioperative care has an important role in cancer survival and suggest modifying their current practice (1388). 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 (1389).
Kim concludes that amide type local anaesthetics increase NK cell activity. Anaesthetics such as propofol and locoregional anaesthesia, which decreases surgery-induced neuroendocrine responses through the hypothalamic-pituitary-adrenal axis and sympathetic nervous system suppression, may cause less immunosuppression and recurrence of certain types of cancer compared to volatile anaesthetics and opioids (1390).

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 (1391).
O'Dwyer and colleagues support the concept that consideration should be given to anaesthesia techniques and perioperative treatments. Although not immediately harmful, they may be associated with poor outcomes temporally distant from the treatment, secondary to induced immunosuppression (1392).
Iwasaki and co-workers report that increasing evidence shows that anaesthesia and adjuvant locoregional techniques may have an impact on cancer growth and/or progression. However, they claim that there is not sufficient evidence to support an alteration of current clinical practice and that further research is warranted (1393).
Vaghari et al. expand further on the role of regional anaesthesia-analgesia in preservation of immune function (1394).

Kurosawa states that accumulated basic and clinical data suggest that total intravenous anaesthesia with propofol, cyclooxygenase antagonists, and regional anaesthesia can decrease negative consequences associated with perioperative immunosuppression. On the

other hand, volatile anaesthesia, systemic morphine administration, unnecessary blood transfusions, intraoperative hypoxia, hypotension, hypothermia, and hyperglycaemia should be avoided (1395).
Hiller's group expands further on perioperative events potentially influencing cancer recurrence risk following surgery (1396).

Sun et al. have performed a systematic review and meta-analysis in which they have evaluated the effects of perioperative regional anaesthesia and analgesia on survival and cancer recurrence after cancer surgery. Perioperative regional analgesia use was associated with improved overall survival following cancer surgery. However, no association was detected with respect to cancer recurrence (1397).
In their meta-analysis, Grandhi, Lee and Abd-Elsayed also failed to identify any benefit of regional anaesthesia on overall survival, recurrence –free survival, or biochemical recurrence-free survival (1398).

Le-Wendling and colleagues state that the benefits of regional anaesthesia in reducing cancer recurrence have a sound theoretical basis, and in certain cancers, are supported by the existing body of literature (1399).
Byrne et al. also conclude that current laboratory research suggests that perioperative interventions may impact recurrence or metastasis through effects on cancer cell signalling, the immune response, or modulation of the neuroendocrine stress response. With limited data upon which to make strong recommendations, the authors state that anaesthesiologists should seek optimal anaesthesia and analgesia for their patients based on individual risk-benefit analysis and best available evidence on outcomes other than cancer recurrence (1400).
Green and Tsui state that recommendations for a specific anaesthetic technique based on cancer outcome alone cannot be made. A pragmatic solution would be to offer regional anaesthesia in isolation or combined with propofol infusion to cancer patients if appropriate and if local expertise is available. Regional anaesthesia offers excellent analgesia, a low incidence of postoperative nausea and vomiting, and a favourable immunological profile based on current understanding of laboratory evidence (1401).

Sekandarzad cum suis conclude that the perioperative period in the cancer patient represents a unique environment where surgically mediated stress response leads to immune suppression. Regional anaesthesia techniques when indicated in combination with multimodal analgesia that includes NSAIDs, opioids, and local anaesthetics to prevent the pathophysiologic effects of pain and neuroendocrine stress response should be viewed as an essential part of balanced anaesthesia (1402).

Tohme, Simmons and Tsung expand further on the effects of surgery on cancer (1403).

Consequently and in contrast to for instance Heaney et al. (1404), Xuan et al. (1405), Cakmakkaya et al. (1406), the published Consensus statement from the BJA Workshop on Cancer and Anaesthesia (1407), Jakobsson and Johnson (1408), and Ciechanowicz and Ma (1409), 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.

The anesthesiologist has to be aware that anaesthetic agents and anaesthesia techniques may have a significant impact on tumour evolution (1410,1411).
Consequently, we support Cassinello's conclusion that anaesthesiologists should follow current best clinical practice and include all strategies that effectively decrease pain and attenuate stress. Regional anaesthesia and multimodal analgesia, adding anti-inflammatory drugs, plays an unquestionable role in the control of perioperative pain and may improve recurrence-free survival (1412).

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 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 to play a central role in

tumour growth and metastasis, perhaps that by using specific anaesthetics the anaesthesiologist will be able to fight cancer in a proactive manner.

Horowitz and colleagues offer an interesting overview of the impact of the perioperative period on long-term cancer outcomes (1413).
Kim expands further on this issue (1414).

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

- General anaesthesia combined with adequate multimodal perioperative analgesia, with the aim to attenuate the surgical stress response and 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 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 (182-185). Fortunately, the tumour-enhancing effects of S-ketamine can 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 more pronounced tumour inhibiting properties (58-60).

- 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.

- 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. Thus reducing the need for volatile anaesthetics. 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 readily feasible for this type of surgery, one could theoretically expect beneficiary effects of perioperative intravenous administration of lidocaine. Partly because of its opioid reducing effects, partly because of the anti-tumour properties of amide-linked local anaesthetics. 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 100 µg of sufentanil. 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 amide-linked local anaesthetic, like ropivacaine, suffices to attenuate the stress response and 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.
  We share the view that adjuvant locoregional analgesia should be administered using ultrasound. Thus achieving better postoperative pain scores and reducing the requirement of additional opioids (1415).

  In case of more extensive thoracoscopic surgery, like for instance pleurodesis, we recommend thoracic epidural analgesia combined with general anaesthesia. Partly for its more pronounced analgesic effects, but also in view of a more adequate attenuation of the surgical inflammatory stress response.

- 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 to regulate the depth of anaesthesia.

- Co-medication with paracetamol and NSAIDs like diclofenac (in the absence of contra-indications for the use of NSAIDs and/or 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.

- Theoretically, one could expect beneficiary effects of simultaneous intravenous administration of lidocaine. Partly because of its opioid reducing effects, partly because of the anti-tumour properties of amide-linked local anaesthetics. Unfortunately, no study results have been published at this stage that back-up these assumptions. Further study results have to be awaited.

II.3 In case of breast cancer:

- Especially in the case of breast cancer surgery, it appears to be advisable to attenuate the surgical stress response as much as possible and to reduce the use of opioids without affecting pain perception.

- 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 and to attenuate the stress response (1416). 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% (1417).

- 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 surgical stress response. In our experience, field blockade alone reduces opioid consumption inadequately in case of extended 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 followed by direct reconstruction of the breast is a matter of discussion in our department and is currently being investigated. Evidence so far suggests that ropivacaine may be 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 an NSAID, like diclofenac, appears to be more than reasonable.

- Standard administration of dexamethasone 4-8 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 and PECS I and II blockades may hold a future role in breast cancer surgery. Further study results on their effectiveness in surgical oncology have to be awaited.

- The same applies for treatment with intravenous lidocaine. However, recent study results showed little beneficiary effects of intravenous lidocaine on opioid consumption, pain score, and postoperative nausea and vomiting (PONV), fatigue and or duration of postoperative hospital stay (561,598,600,651,658,659,1153,1281, 1286). Once more, further study results have to be awaited.

- 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 (limited) 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 (1418). Apart from its analgesic effects, a significant reduction of bladder spasms has been reported in laparoscopic surgery of the bladder and/or prostate. Furthermore, evidence shows that TAP blockade attenuates the surgically induced stress response. There is also evidence that ropivacaine is the local anaesthetic of choice for TAP blockades in laparoscopic surgical oncology (58,59). Unfortunately, both the analgesic effects (reduced opioid use) and the attenuation of the stress response appear to last for a relatively short period of time and do not exceed the first postoperative day (1419,1420).
  Once again, in our view, adjuvant locoregional analgesia should be administered ultrasound-guided, if possible.

  In case of more extensive laparoscopic surgery, which is accompanied by a more marked surgical stress response, we recommend general anaesthesia combined with thoracic epidural analgesia. The ratio for doing so lies in the fact that epidural analgesia attenuates the stress response to a greater extent and during a longer period of time compared to TAP-blockade. Although postoperative immune function is better preserved in patients after laparoscopic-assisted surgery than after open surgery, the introduction of pneumoperitoneum alone results in a significant stress response (905). In our opinion, one should take these effects during laparoscopic surgery into account when deciding which anaesthetic technique should be used with respect to the attenuation of the stress response.
  In each case, the advantages of a more profound and longer lasting attenuation of the stress response and the disadvantage of increased invasiveness should be balanced.

- In case of laparotomy, we recommend general anaesthesia combined with thoracic 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 lower 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 (966).

In case epidural analgesia is contraindicated or (technically) not possible, the administration of S-ketamine can be considered. Once more, it must be emphasized that S-ketamine has been shown to stimulate the beta-adrenergic system with possible subsequent adverse oncologic effects. Simultaneous beta-blockade might therefore be considered. Unfortunately, there are no data available on the required level of beta-blockade in surgical cancer patients receiving S-ketamine.

- For laparoscopy as well as laparotomy, the same recommendations apply for the type of general anaesthesia and co-medication with paracetamol and diclofenac. However, it has to be mentioned that the use of diclofenac, especially in the setting of non-elective surgery, may be associated with a greater risk for anastomotic leak in case of anastomosis of the ileum and possibly the 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 thoracic epidural analgesia in elective surgery.

  In case of anastomosis of the proximal colon or the ileum, the use of NSAID’s in conjunction 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. In our opinion, as far as colorectal surgery is concerned, 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 in an elective setting.

- 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.

- Theoretically, one could also expect beneficiary effects of simultaneous perioperative intravenous administration of lidocaine. However, a recent Cochrane study indicates that there is low to moderate evidence that perioperative continuous intravenous infusion of lidocaine, when compared to placebo, has an impact on pain scores and/or postoperative nausea. Furthermore, there is also limited evidence that this intervention has further impact on other relevant clinical outcomes, such as gastrointestinal recovery, length of hospital stay, and opioid requirements (68,561,563,598,600,657-659,1153,1281). Obviously, further study results have to be awaited.

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 also because of the previously described tumour inhibiting effects of amide-linked local anaesthetics. 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) thoracic epidural analgesia combined with intravenous propofol sedation when necessary.

II.7 Since very little is known in relation to anaesthetic support in transarterial chemo-embolization of the liver (TACE), we follow the recommendations postulated by Giammaria Fiorentini et al (1376):

- 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 mention, 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 sufentanil 100 µg 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.

- One could consider administering parecoxib perioperatively to improve postoperative pain control following this procedure (1377).

II.8 Chemosaturation

We could only find one study focussing on the anaesthetic considerations regarding this procedure (1384). 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. Until 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 appears to be 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 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 cardiovascular, cerebrovascular and pulmonary conditions.

Recent study results even suggest that NLR is an independent indicator of short- and long-term mortality in critically ill patients, and prognostic of cancer, acute kidney injury in

septic patients, bacteriaemia and sepsis, cardiovascular, cerebrovascular mortality and pulmonary diseases (1421-1442). For instance, Giede-Jeppe et al. state that NLR represents an independent parameter associated with increased mortality in patients with spontaneous intracerebral haemorrhage. Therefore, stroke physicians should focus intensely on patients with increased NLR, as these patients appear to represent a population at risk for infectious complications and increased short-term mortality (1438).
A recent study even demonstrates that NLR can be used as an independent predictor of acute myocardial infarction in patients with renal insufficiency, in whom troponin assays are affected by the elevated serum creatinine (1443).

Caimi and co-workers report that in juvenile acute myocardial infarction patients mean NLR value was significantly increased compared to normal controls. However, NLR did not discriminate between STEMI and non-STEMI, or diabetics and non-diabetics. NLR did discriminate between smokers and non-smokers (1444). The effects of smoking on NLR are are endorsed by Al's study results (251).

Kalelioglu et al. even claim that NLR might play an important role in certain psychiatric disorders as well (1445).
Toptas and colleagues endorse the prognostic value of NLR (and PLR) in patients with acute mesenteric ischaemia (1446).
Venkatraghavan and co-workers have investigated the prevalence of elevated NLR in preoperative patients and report an elevated NLR (> 3.3) in 26.6% of all preoperative patients. Furthermore, malignancy proved to be a constant predictor of elevated NLR (> 4.5) (1447).

In fact, Kumar and colleagues claim that NLR (> 3.0) is a validated independent prognostic factor for overall survival in cancer patients treated in phase I trials with no association with therapeutic steroid use (1448).
Nakamura et al. have studied the prognostic value of NLR in terminal cancer patients and they report that NLR appears to be a useful and simple parameter to predict the clinical outcomes of patients with terminal cancer (1449).

Mitsuya's group reports that an elevated NLR (≥ 5.0) is a predictor of worse survival after resection of brain metastases (1450).
Nishijima and co-workers even suggest that frailty and inflammation might be associated with each other in older patients with cancer (1451).

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 indications that even symptomatic treatment of the (surgical) inflammatory stress response might 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 suggest 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 the (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.

As mentioned previously, anaesthesia has evolved spectacularly over the last few decades. However, this was achieved by gradually adapting our clinical practice and not by endorsing the status quo. 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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