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DISSERTATION

Influence of selective neurogenic blocks on long-term survival of patients undergoing lung resection

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Aus der Klinik für Anästhesiologie m.S. operative Intensivmedizin
Der Medizinischen Fakultät Charité – Universitätsmedizin Berlin
– Direktorin: Univ.-Prof. Dr. med. C. Spies –

Abstract

Influence of selective neurogenic blocks on long-term survival of patients undergoing lung resection

Markus Renius

OBJECTIVE: A double-blind, prospective, randomized, controlled trial was performed to examine the effects of thoracic epidural block, intravenous remifentanil and intravenous clonidine on the postoperative Th1/ Th2-ratio after lung surgery. This study aims to analyze the influence of the intervention on long-term survival and possible predictors.
METHODS: 60 patients were randomized into three groups to receive either remifentanil intravenously (remifentanil-group, n=20), remifentanil and clonidine intravenously (clonidine-group, n=20) or ropivacaine epidurally (ropivacaine-group, n=20) during lung resection. Six years after the operation of the last patient the days of survival of all patients were quantified.
RESULTS: Neither a difference nor an equivalence of the three therapy arms on long-term survival can be proven, while useful predictors can be identified.
CONCLUSION: While intraoperative thoracic epidural block decreases the IFN-γ/ IL-4 ratio immediately after lung surgery, an influence of neurogenic blocks on long-term survival could not be proven.

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Zusammenfassung

Einfluss selektiver neurogener Blockaden auf das Langzeitüberleben von Patienten, die sich einer Lungenresektion unterzogen haben

Markus Renius

ZIELSETZUNG: Es wurde eine doppelblinde, prospektive, randomisierte, kontrollierte Studie durchgeführt, um den Einfluss eines epiduralen Blocks, einer intravenösen Remifentanilgabe und einer intravenösen Clonidingabe auf das postoperative Th1/ Th2-Verhältnis nach einer Lungenresektion zu untersuchen. Diese Arbeit untersucht den Einfluss der Intervention auf das Langzeitüberleben und mögliche Prädiktoren.
METHODEN: Es wurden insgesamt 60 Patienten randomisiert, um während der Lungenresektion doppelblind entweder 1) Remifentanil intravenös (Remifentanil-Gruppe, n=20), oder 2) Remifentanil und Clonidin intravenös (Clonidin-Gruppe, n=20) oder 3) Ropivacain epidural (Ropivacain-Gruppe, n=20) zu erhalten. Sechs Jahre nach der Operation des letzten Studienpatienten wurden die postoperativ überlebten Tage bei allen Patienten registriert.
ERGEBNISSE: Es konnte weder ein Unterschied noch eine Äquivalenz der Therapiearme in Bezug auf das Langzeitüberleben nachgewiesen werden, wohingegen nützliche Prädiktoren identifiziert werden konnten.
SCHLUSSFOLGERUNG: Obwohl der intraoperative epidurale Block das IFN-γ/ IL-4 direkt nach der Lungenresektion vermindert, konnte ein Einfluss der neurogenen Blockaden auf das Langzeitüberleben nicht gezeigt werden.

1 Introduction and Background

1.1 The Patients

With lung cancer remaining by far the number one cancer-related death worldwide,(1) the collective of lung cancer patients is both of particularly relevant size as well as so seriously threatened by the late detection, by the overwhelming aggressiveness and lethality of their disease, by their comorbidity and by the lung surgery itself, that an operation is the best option for less than 20-25%.(2) Typically this collective is predominantly male, with a median age of 60-65 years and often suffering from systemic morbidity such as cardiovascular disease and chronic lung disease.(3)(4)(5)

Lung cancer is the primary reason for lung surgery, followed by metastases, suspected lung cancer and other tumors.(3) Lung surgery introduces risks such as surgical trauma, permanent reduction of surface interface, perioperative infections and fistulae, pain, delirium, blood loss, cardiac arrhythmia, postoperative nausea and vomiting and the need for intensive care or monitoring in an intensive care setting.(5) Additional difficulties arise from the overlap of the operation field and the ventilation, which gave rise to the technique of one lung ventilation and which in turn adds further burdens such as the temporary reduction of the surface area of the interface, clinically relevant right-to-left shunt, elevated afterload for the right heart due to hypoxic pulmonary vasoconstriction and increased complexity of establishing and maintaining a secure airway.(6)(7)(8)

Accordingly, investigations are needed to determine the optimal means to support these patients during the perioperative period. Therefore, a clinical trial was performed between 2006 and 2008 whose primary objective focused on the changes of the immunological homeostasis depending on the type of the intraoperative neurogenic block.(9) Another objective is the analysis of the outcome in terms of long-term survival which will be described in the following.

1.2 The Intervention

There has been a long and ongoing debate about the impact of the anesthetic regime on patient outcome. TEB (thoracic epidural block) is considered by many to be the gold standard for lung surgery,(10) though this matter is still under discussion.(11) Recently, a solid case was made for it in the editorial of Annals of Surgery(11) where the implications of the meta-analysis of Pöpping et al. were discussed. This meta-analysis favors epidural anesthesia in combination with general anesthesia over general anesthesia alone when postoperative morbidity and mortality is considered,(12) but data from prospective, randomized trials which measure the impact of different anesthetic regimes during lung surgery on long-term survival is lacking.

The anesthetic regime consists primarily of hypnosis, analgesia and muscle relaxation. While intraoperative hypnosis within this study was sustained by default through intravenous infusion due to the - still disputed - unwanted effects of inhalational anesthetics(13)(14) and to a pragmatic approach to reduce exposure of personnel to volatiles during the complex management of the airway, several alternatives are available for intraoperative analgesia, such as epidural anesthesia (with or without epidural administration of opiates or other epidurally applicable drugs) and continuous intravenous administration of remifentanil or other opiates, possibly in combination with other analgesic drugs and even the combination of both epidural and intravenous analgetic drugs, which is the most common among them. Thus the question arises as to which kind of analgesia can be proven to be superior to the others, with a seldom clinically used, rather experimental variant in form of a combination of continuous intravenous remifentanil and an intravenous sympathetic block by intravenous clonidine as a further alternative that is being investigated as the third therapy arm in this study.

Epidural anesthesia reduces intraoperatively the need for both additional pharmacological muscle relaxation and systemic opioids and also blocks sympathetic innervation in a selective portion of the body.(15)(16) It reduces the need for prolonged intubation or reintubation while improving lung function and blood oxygenation.(17)(18) This offers the benefit of potent postoperative analgesia(19)(18), avoiding the sedative effect and the depressing impact on the respiratory system of systemically administered opiates, while ensuring painless coughing to clear infectious sputum from the lungs, avoiding atelectases and allowing the best ventilatory excursion in the early

postoperative period.(20) These advantages are expected to translate to a lower perioperative infection rate,(17) lower postoperative pain levels, less chronification of pain, less postoperative nausea and vomiting,(12) less complications of other kinds (from deep vein thrombosis and pulmonary embolism to transfusion requirements),(21) more comfort for the patient and better integration into a fast-track approach with early mobilization and a shorter hospital stay,(22) and enhanced functional capacity and health-related quality of life in the weeks after the operation.(23) Furthermore, beneficial effects on inflammation,(9) the electrical conduction system of the heart,(12) coagulation,(24) reperfusion,(25) cardiovascular(26)(27)(28), endothelial(29) and gastrointestinal function(23)(30) have been shown.

On the other hand, there are contraindications for the placement of an epidural catheter, and it has to be considered whether the additional time, personnel expenditure, cost and the risk of both frequent(17) and rare complications are justified by the benefits,(12) with frequent complications being arterial hypotension, pruritus, urinary retention and motor blockade(12), and rare complications being severe nerve damage, severe cardiotoxic or neurotoxic effects or allergic reactions.

Another therapeutic option is the paravertebral block, which is valuable in cases where contraindications won't allow TEB, and increasingly data has been gathered that shows its superiority in some categories compared to TEB.(31)

Alternative approaches, which can be subsumed under the term non-intubated thoracic surgery (NITS) and which have in common that spontaneous ventilation is maintained, include intercostal blocks with or without sedation, epidural anesthesia with or without sedation (also known under the term "awake epidural anesthesia" or "awake thoracic surgery") and laryngeal mask with sedation, but in thoracic surgery all of them are still primarily used in less complex and less invasive surgical procedures(32) or in high-risk patients who are not eligible for other anesthetic techniques.(33) Further variants or additions with or without the corresponding catheter include intrathecal analgesia, intrapleural instillation of local anesthetics, intercostal blocks (non-paravertebral), local infiltration, systemic local anesthetics and cryoanalgesia.(34)(35)(36)

The concept of neurogenic blocks which can be used for the understanding of the function of both regional anesthesia and systemic analgesic agents broadens the concept of analgesia and includes afferent and efferent activity, immunological reflexes and modulation of the vegetative nerve system.(37)

1.3 The Outcome

It has already been shown that intraoperatively epidural anesthesia causes a significantly altered perioperative immune response (which normally consists of an initial hyperinflammation and a consequential overcompensatory response) when compared to remifentanil and the combination of remifentanil and clonidine.(9) Now the answer should be answered if this translates into a difference in survival as well.

Of all the possible endpoints that are of medical interest when therapies are compared (such as length of stay, quality of life, perioperative infections, rate of revision and patient's contentment), a strong emphasis is on long-term survival. Besides the economic cost and immediate postoperative medical condition and surrogate parameters, the years that someone lives after an intervention are of primary importance. This is also reflected by the fact that long-term survival was the most favored topic of the scientific community when the initial results of the clinical trial were presented at various conventions.

Among various survival rates of long-term survival, five years is both the most common as well as the most adequate one because five-year survival in lung cancer patients ranges from 7%-21% according to the region surveyed,(38) with the corresponding survival rate of patients with NSCLC (non-small-cell lung cancer) who undergo complete surgical resection being only 40-50%.(2)

2 The Goal of the Study

The primary goal of this study is to find out:
What effect in adult patients without severe cardiovascular or any immunological disease who undergo any thoracoscopic or open lung resection does analgesia in lung resection in the form of epidural ropivacaine in comparison to intravenous remifentanil in comparison to intravenous remifentanil in combination with intravenous clonidine have on long-term survival?(39)

The secondary goal of this study is to find out:
Which predictors for long-term survival can be measured in adult patients without severe cardiovascular or any immunological disease who undergo any thoracoscopic or open lung resection?(39)

3 Materials and Methods

Major parts of the materials and methods of this study are already published in a publication that describes other aspects of the clinical trial.(9) In the following, these major parts are complemented with the description of all materials and methods involved in the testing of the hypotheses of the present study. In order to honor the copyright of the publishing journal, already published sections are in quotations with minor changes only for better wording where appropriate or changes in the numbering of tables and graphs.

3.1 Approval by the Ethics Committee

“This double-blinded, prospective, randomized, controlled trial was registered in the European Union Drug Regulating Authorities Clinical Trials database (EudraCT 2005-001456-20) and in the International Standard Randomised Controlled Trial Number register (ISRCTN 47414487). The study was approved by the local ethics committee “Ethik-Kommission des Landes Berlin” (registration No. EA 1/175/05) and the German Federal Institute for Drugs and Medical Devices “Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn” (BfArM-No 4030867). Quality of randomization and double-blinded procedure as well as good clinical practice (GCP) conformity was supervised by the contract research organization (CRO) Koordinierungszentrum Klinische Studien Charité (KKS Charité).”(9)

A second approval by the ethics committee of the Charité - University Medicine Berlin was obtained in order to measure the long-term survival of the study patients (EA1 287/15).

3.2 Patient Recruitment

“Consecutive patients scheduled for elective lung surgery at the Charité Campus Mitte Hospital, Charité - University Medicine Berlin were screened for eligibility with the goal of recruiting 60 patients. According to the clinical trial protocol, patients meeting at least one of the following exclusion criteria were not admitted to this study: 1) age under 18 years, 2) guardianship/ conservatorship, 3) refusal to participate in the study, 4) pre-

existing changes of the immune system such as infections meeting the criteria of the CDC (Centers for Disease Control and Prevention) and/ or treatments and disorders with direct influence on the immune system such as immune modulating therapy or adrenal pathology, 5) pregnancy, 6) contraindications for epidural catheter insertion, 7) contraindications for the application of clonidine, ropivacaine or remifentanil, 8) pre-existing treatment with the above-mentioned trial drugs or drugs belonging to the same pharmacological group within a month prior to the operation, 9) heart failure class III or higher according to the NYHA (New York Heart Association) Functional Classification, 10) myocardial infarction in the last eight weeks before surgery.

Written informed consent was obtained from all participants."(9)

3.3 Surgical and Anesthetic Procedures

3.3.1 Lung Cancer as the Main Indication for Lung Surgery

Lung cancer is one of the most common and also one of the most serious cancers. It is one of the most prevalent causes of death and the most common cause of death among cancer deaths worldwide. Its incidence is rising with an estimated 1.8 million lung cancer cases in 2012.(1) It is caused to a large degree by human made pathogenic substances, mainly active and passive smoking of cigarettes and emissions from industry (including occupational exposure), transportation, agriculture, heating and cooking, which are two groups of factors which have been reduced in some regions of the world, while they are a growing problem in others.(1) Changes in these two areas that take place outside of the medical system are more effective than any known changes in medical prevention, diagnosis and treatment of the disease, including smoking-cessation interventions, which fail to show an effect on cessation rates.(40) Other factors include a family history of cancer, an unhealthy diet, male gender, lower education level, exposure to radon and chronic obstructive pulmonary disease.

The different entities of lung cancers are grouped based on their histology into types of SCLC (small-cell lung cancer), NSCLC and other lung tumors such as other primary tumors of the lung (pulmonary carcinoid tumors, pleuropulmonary blastoma, neuroendocrine tumors, glandular tumors, lymphomas, sarcomas, vascular tumors of

the lung, undifferentiated tumors or combinations thereof), lung metastases of other cancers or invasive mediastinal or pleural cancers. The group of NSCLC can further be divided into adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma.

The stage of a lung cancer refers to the extent to which the cancer has spread from its original source to the rest of the body. Staging is a way to estimate a prognosis and decide whether curative or palliative therapy is indicated. It is performed using the TNM classification (Tumor - Nodes - Metastases), evaluating the size and localization of the primary tumor, the metastases in regional lymph nodes and distant metastases. Individual staging is subject to change, as preoperative imaging studies don't have the same reliability as the surgical examination of the intraoperative situs and the intra- or postoperative histological analysis that is performed by the pathologist.

Treatments of lung cancer include surgery, radiation therapy and chemotherapy, including targeted therapies and combinations thereof. More experimental strategies like immunotherapy and epigenetic therapies are being researched or in the process of approval.(41)(42)

Lung cancer is known for its bad prognosis, as the illness tends to be diagnosed at a late stage, making a cure unlikely. The typical symptoms such as coughing, chest pain, weight loss, fever, fatigue, dyspnea, nerve damage and paraneoplastic phenomena are both late and/ or too unspecific to allow for timely therapy, making incidental findings the most promising cases. Once lung cancer is presumed, chest x-rays, computer tomography and/ or positron emission tomography are used to substantiate and a biopsy to confirm the presumptive diagnosis. The window of opportunity for a cure is primarily not closed due to the size of the tumor or its destruction of vitally important lung tissue but by its formation of metastases in the brain, bone, adrenal glands, other lung tissue of the ipsilateral or contralateral lung, liver, pericardium and kidneys. Possible strategies for the future are therefore the much debated low-dose CT scans (X-ray computer tomography) for high-risk individuals as well as the more promising development of biomarkers for early detection of lung cancer.(43)(44)

Lung cancer is the most common indication for lung resection. Therefore, any study that investigates possible improvement of perioperative care of patients who undergo lung

resection also deals with the question whether the therapy of this very common cause of death can be improved.

3.3.2 Methods of Lung Surgery

Several approaches to resecting lung tissue are possible, with VATS (video-assisted thoracoscopic surgery) and thoracotomy as the two main techniques. VATS can be scaled up to a thoracotomy or a minimal thoracotomy, where the surgical incision in the chest wall is shorter than a surgical incision of a conventional thoracotomy, as it only serves to enable one specific step of the operation such as the salvage of the resected tissue and no other steps such as orientation within the thorax or resection of the tissue. While a conventional thoracotomy results in a large trauma (both in soft tissue and ribs) accompanied by higher intraoperative and postoperative pain levels, higher stress levels with consequential stronger proinflammatory stimulation and antiinflammatory counteregulation, a VATS produces very small wounds, with a minimal thoracotomy in between the two procedures. A thoracotomy can result in breaking one or more ribs due to the surgical procedure of prying open the chest, possibly aggrevated by coughing by the patient, which can be caused by insufficient anesthesia. Broken ribs, tissue trauma and postoperative pain can result in an involuntary inhibition of the patient to cough in the postoperative period, which can cause atelectasis, retention of sputum and consequential pneumonia.

3.3.3 Anesthesia for Lung Surgery

The purpose of Anesthesia in lung surgery is to immobilize the patient, enabling the surgeon to reach the intraoperative site with minimal spatial restrictions, protect the patient from pain, discomfort and awareness and to maintain equilibrium of vital body functions.

3.3.3.1 Thoracic Anesthesia and One Lung Ventilation

Surgery within the pleural cavity makes it necessary to ventilate only one lung while using the space which is normally taken up by the other lung (which is collapsed in order to provide this space) to gain access to surgical sites (such as structures

neighbouring the lung) and/ or to operate on the collapsed lung while protecting the ventilated lung from blood, secretion, pathogens and malignant cells of the other side that may be transferred via the main bronchi. This procedure is called lung isolation. Historically, two concepts have been established to attain this goal, the double lumen tube and the bronchial blocker, while a third concept, namely the vacuum chamber, forces the surgeon to operate on the lung without its complete collapse and without protection of the ventilated lung from transfer of unwanted material. All three concepts have advantages and disadvantages.

The double lumen tube allows CPAP (continuous positive airway pressure) ventilation of the collapsed lung in case of severe hypoxia and selective suction cleaning in both bronchi. It has the disadvantage of a higher risk of injury of the trachea, carina and bronchi due to the rigid form of the preformed tube and its mandrin, and this risk increases with any movement of the patient, especially when coughing. The difficulty of placing the tube is greatly increased in situations where the patient presents a difficult airway and/ or if there is an indication to perform a rapid sequence induction. Nevertheless, it is possible to try to counteract these problems by using bronchoscopy to guide the double lumen tube to its final position once it has passed the larynx. Double lumen tubes vary in their sizes and in their orientation; there are left sided and right sided versions, with the right sided versions having a Murphy eye that is merged with the bronchial cuff which has to be placed on the opening of the bronchus of the right upper lobe in order to secure the ventilation of the right upper lobe. If a pneumonectomy of the left lung makes it impossible to use a left sided double lumen tube, it is still possible to choose a tube with the opposite orientation.

The bronchial blocker has the advantage of being less invasive. It makes it possible to isolate individual lobes. On the other hand, it is not possible to use it for pneumonectomy, and neither suction nor ventilation is possible in the blocked bronchus. Without the possibility of selectively applying suction to the blocked lung, the risk of contamination of the opposite lung with blood, secretion, pus or cancer cells is elevated. While a double lumen tube allows one lung ventilation even if the tube is placed in the wrong bronchus, the bronchial blocker requires proper positioning.

The vacuum chamber is a third option to operate on the lung. It was invented and introduced into clinical practice by Ferdinand Sauerbruch in 1904. Its operating expense and technical difficulties exceed by far those of the other two options and it has little practical significance at the moment, even though experiments with negative pressure ventilation in general show promising - though disputed - results.(45)(46)

3.3.3.2 Thoracic Anesthesia and Epidural Blocks

While epidural anesthesia shows many promising effects, ranging from less endothelial injury(29), altered antioxidant markers(47) and stabilized levels of plasma nitrite(48) to improved postoperative analgesia(20), it is also associated with risks such as hypotension, accidental dura puncture with consequential PDPH (post-dural-puncture headache), accidental spinal anesthesia with possible total spinal anesthesia, high epidural block, epidural hematoma, epidural abscess, other forms of infection, spinal injury and other neurological lesions, accidental systemic application of local anesthesia due to intravascular malposition with consequential intoxication as well as possible damage to the catheter (primarily during insertion) which can lead to catheter fragments remaining in the body.

There are additional practical considerations, such as a mismatch of the blocked dermatomes and the surgical wound or a malposition that results in a missing or attenuated or one-sided analgesic effect. While allergic reactions to local anesthetics used in epidural anesthesia have been described, it must be emphasized that their rate of occurrence pales in comparison to other analgesic drugs such as metamizole.(49) As with all analgesic agents, the required dose for sufficient analgesia through epidurally administered local anesthetics is different in each individual, which makes it necessary to adjust the therapy to the patient being treated.

3.4 Study Medication

All three drugs that serve as intervention in the trial are well known and routinely used in the clinical setting.

3.4.1 Epidural Block

Ropivacaine is a local anesthetic drug of the amino amide type which is used for epidural anesthesia (including caudal epidural anesthesia and continuous/ intermittent application through an epidural catheter, both intra- and postoperatively), spinal anesthesia, nerve blocks and infiltration. It has less cardiotoxicity than bupivacaine and is usable both as a racemate and the S-enantiomer, the latter being marketed in the form of a hydrochloride by Astra Zeneca under the trade name Naropin ©. Contraindications include known allergies triggered by a local anesthetic of the amid type, intravenous local anesthesia and extensive use in hypovolemic patients. High doses of ropivacaine lead to central nervous complications of varying severity (such as convulsions) as well as cardiotoxic effects. These symptoms are enhanced in case of erroneous intravenous application and may be masked by general anesthesia. Side effects have to be separated into several groups: Firstly, there are side effects associated with the positioning of the epidural catheter. These include infections, accidental intrathecal insertion or hematoma. These side effects affect all three therapy arms as every patient in the trial receives an epidural catheter before operation. Secondly, there are side effects due to the nerve block, which can lead, via bilateral selective thoracic sympathectomy, to hypotension and bradycardia. Thirdly, there are side effects which are caused by the drug when it is absorbed, entering other compartments of the body. The latter is intensified by high doses and accidental intravascular injection, possibly leading to systemic toxicity. Measures that can be taken to avoid systemic administration include the test dose after insertion, assessment of and communication with the patient, repeated aspiration of the catheter and vigilant ECG (electro-cardiography) monitoring.

3.4.2 Central α2-Agonist

Clonidine acts as a sympatholytic drug through its stimulation of central α2-receptors, a mechanism it shares with dexmedetomidine. Its elimination half life is 10-20 hours. It is used in agitated patients suffering from alcohol withdrawal, in patients with hypertension in combination with other antihypertensive drugs, in a wide variety of off-label indications such as in ADHD (attention deficit hyperactivity disorder) and various psychiatric and neurological disorders, as a sedative in intensive care, as analgesia, as an additive in epidural anesthesia or spinal anesthesia and in the treatment of the

restless legs syndrome as well as rosacea. Contraindications include allergies against clonidine or any other ingredient of the marketed formulation, dysfunction of the electrical generation and conduction system of the heart (such as sinus bradycardia and heart blocks), a heart rate under 50 beats per minute, major depression and pronounced hypotension.

Furthermore, clonidine should only be administered under thorough medical supervision if patients are diagnosed with coronary artery disease, recent myocardial infarction, severe heart failure, severe peripheral artery disease, Raynaud's phenomenon, thromboangiitis obliterans, kidney failure, cerebrovascular insufficiency, constipation and polyneuropathy. The minimal lethal overdose of clonidine in rhesus macaques has been shown to be three orders of magnitude above a common clinical dose for humans.

3.4.3 Opioids

Remifentanil is a short acting opioid with exceptional controllability due to its rapid hydrolysis by nonspecific plasma and tissue esterases. This controllability can be maintained even if high doses are administered for hours; on the other hand, rapid fading of the analgesic effect makes it necessary to combine it with a prophylaxis against hyperalgesia. It is administered solely via continuous intravenous infusion with the intention to sedate or anesthetize patients. As a selective μ-opioid receptor agonist, it shows a higher potency than alfentanil while generating similar pharmacological effects(50). When combined with hypnotic agents it allows a reduction of the latter because of synergistic effects. It is marketed in the form of a hydrochloride by Glaxo Smith Kline under the trade name Ultiva©. Because it contains glycin, it must not be administered into the intrathecal compartment. It should not be given as the only drug to induce anesthesia. Contraindications are allergies against remifentanil or any other ingredient of the marketed formulation.

3.5 Study Protocol

"According to the investigational protocol, patients were randomized in three groups to receive either remifentanil intravenously (remifentanil group) or remifentanil and clonidine intravenously (clonidine group) or ropivacaine epidurally (ropivacaine group) in

a double blinded fashion. Independent pharmacists assigned the patients to the different groups according to a computer-generated randomization list based on block randomization (six patients per block) and supplied trial drugs and placebo in identical-appearing coded syringes as shown in Table 1. Without exception, all study personnel and participants were blinded to treatment assignment for the whole duration of the study and they were not informed about the block sizes.

Disguised Syringes	**Remifentanil Group**	**Clonidine Group**	**Ropivacaine Group**
10 ml syringe for epidural bolus application	10 ml of placebo	10 ml of placebo	10 ml of **ropivacaine** 0.75% (75 mg)
10 ml syringe for intravenous bolus application	10 ml of placebo	1 ml of **clonidine** (150 µg) diluted with 9 ml of normal saline	10 ml of placebo
50 ml syringe for continuous intravenous infusion	10 mg of **remifentanil** diluted with 50 ml normal saline	10 mg of **remifentanil** diluted with 50 ml normal saline	50 ml of placebo
50 ml syringe for continuous intravenous infusion	50 ml of placebo instead of clonidine	500 µg **clonidine** (3,3 ml) diluted in 46,7 ml normal saline	50 ml of placebo
50 ml syringe for continuous epidural infusion	50 ml of placebo	50 ml of placebo	50 ml of **ropivacaine** 0.2% (2 mg/ ml)

Table 1. Blinding of the study medication

“Content of the various types of identical-looking coded syringes that were used for delivery of remifentanil, clonidine or ropivacaine during lung resection surgery in the present study”(9) (permission granted)

After oral premedication with 0.1 mg/kgBW (body weight) midazolam, all patients received epidural catheterization independently of randomization. After local infiltration of 2-5 ml 1% lidocaine, thoracic epidural puncture was performed in the operating room using a median approach by the loss of resistance technique at the level of Th4-Th7. After 5 cm catheter insertion into the epidural space, an accidental subdural catheterization was ruled out by injecting a test dose of 3 ml bupivacaine 0.5%. All lung resections were performed by a lung surgery specialist assisted by at least one senior surgeon. Lung resection was performed using either a lateral thoracotomy approach or VATS depending on the malignancy, size and localization of the lung disease. Anesthesia was performed by a team of anesthesiologists under the supervision of a specialist with a great deal of experience in thoracic anesthesia and in accordance with a standardized protocol.(51) After epidural catheterization, the trial therapy was started. Investigational drugs administration was performed as showed in Figure 1. Postoperative analgesia was performed with TEB using ropivacaine 0.2% and 0.5 µg/ml sufentanil in all patients according to the standardized protocol.(51)”(9)

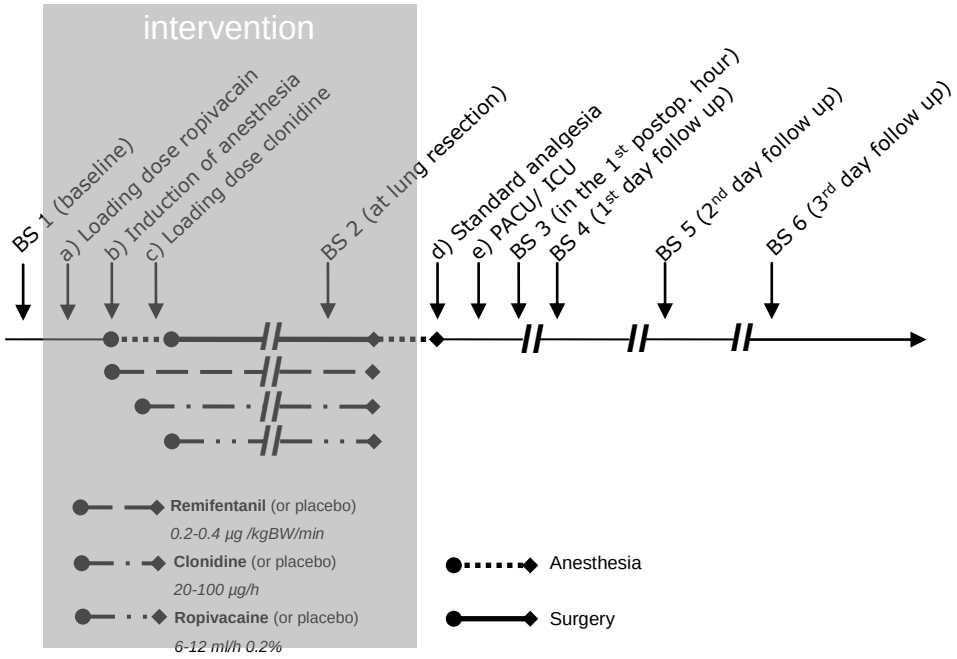

Figure 1. Intervention

“a) Epidural bolus injection of 75 mg ropivacaine 0.75% or placebo; b) Induction of anesthesia with 0.1-0.2 mg fentanyl, 1.5-2.5 mg/kgBW propofol and 0.1 mg/kgBW cisatracurium followed by continuous intravenous infusion of 6-8 mg/kgBW propofol; c)

Intravenous bolus injection of 150 µg clonidine or placebo; d) Intravenous bolus injection of 0.1 mg/kgBW morphine and epidural infusion of 6-12 ml/h 0.2% ropivacaine plus 0.05 µg/ml sufentanil (verum); e) postoperative care at ICU (intensive care unit) or PACU (post anesthesia care unit). BS= Blood Sample”(9) (permission granted)

3.6 Measurement of Postoperative Survival Time

Postoperative survival was measured with an inquiry at the residents’ registration office. The inquiry was performed six years after the operation of the last study patient. This yielded data on all patients who complied with the legal duty to register their current place of residence at the registration office. This data included the date of death in case that the person in question had died in the meantime. When data was not available at the registration office or the registration offices of other districts, the contact address in the electronic medical file at the hospital and the administrations of cemeteries were used to establish whether the person is still alive or not.

The data was entered into the database using the already assigned pseudonyms. An online time difference calculator was used to produce the number of days between the operation (which is not necessarily the day of recruitment) and the date of death, if applicable. Results were tested with regard to their plausibility.

This method can be considered to be prospective because the patient collective is prospectively randomized and the intention to measure the long-term survival was documented a priori before events that were later measured occurred. So while the procedure can be described as retrospective analysis of prospective data the relevant properties of a randomized controlled trial (being the elimination of selection bias and reduction of confounding to random levels) apply, leaving only the fact that the primary goal of the present study wasn’t the primary goal of the clinical trial. This results in the problem of any secondary goal which is best described by the fact that with enough goals examined, one of them inevitably has to reach significance even if the data is random. Therefore, caution should be exercised when it comes to the interpretation of these findings. On the other hand, the unique opportunity to use a randomized trial to answer a multitude of questions should not be missed.

3.7 Measurement of Possible Predictors

Possible predictors such as sex, age, BMI, ASA (American Society of Anesthesiologists physical status classification system), FeV1 (forced expiratory volume in one second), the approach of the surgery (VATS or thoracotomy), the history of smoking and whether a preoperatively known neoplasia was the reason tor the operation were entered into the database according to the CRF (case report form), the anesthesia protocol or the patient file. These entries were made during the clinical trial. The smoking status included pack years, smoking history and present smoking habits, with the last four weeks being the relevant time frame.

3.8 Statistical Analysis

“Descriptive statistics were computed for all study variables. Discrete variables are expressed as counts (percentage) and continuous variables as means ± standard deviation (SD) or median (25th – 75th percentiles), respectively. Because of the small sample sizes, differences between the groups studied in terms of interesting clinical parameters were tested by using non-parametric statistical tests (Kruskal-Wallis tests and Mann-Whitney-U tests, respectively). Frequencies were tested by the chi-square-test in contingency tables. In the case of small samples, greater differences in sample sizes, large but unbalanced groups, data sets containing ties, or sparse data, tests were carried out in an exact version.”(9)

Long-term survival was analyzed with the Kaplan-Meier method (52) and tested for differences with log-rank, Breslow and Tarone-Ware test. However, in order for the survival analysis to have full applicability, the condition of the proportional hazard must be tested. If the proportions of the hazards of the patients in the three therapy arms are constant over time, the Grambsch test will not be significant.

Another problem is to predict the distribution of the time to event (death) from a set of explanatory variables or risk factors, in other words to investigate the influence of such risk factors on survival. Statistical strategies for prediction are similar to those used in ordinary regression. However, in survival analysis we deal with a special type of nonlinear regression, the Cox proportional hazard regression. There are some caveats involved in this proposition.

First of all, the precondition of proportional hazard has to be fulfilled also in the case of the Cox regression. As mentioned above, the proportional hazard condition can be proved by means of the Grambsch test.
Second, even though the data of risk factors is available and the calculation with several covariates possible, the number of covariates must be limited by theoretical considerations.(53)(54)

Numerical calculations were performed with IBM SPSS Statistics, Version 22 (Copyright IBM Corporation, Armonk, New York, United States) and StatXact 6®, CYTEL Software Corp., Cambridge, MA 02139, USA. A value of $p<0.05$ was considered to be statistically significant. All tests should be understood as constituting exploratory data analysis, such that no adjustments for multiple testing have been made.

4 Results

4.1 Screening

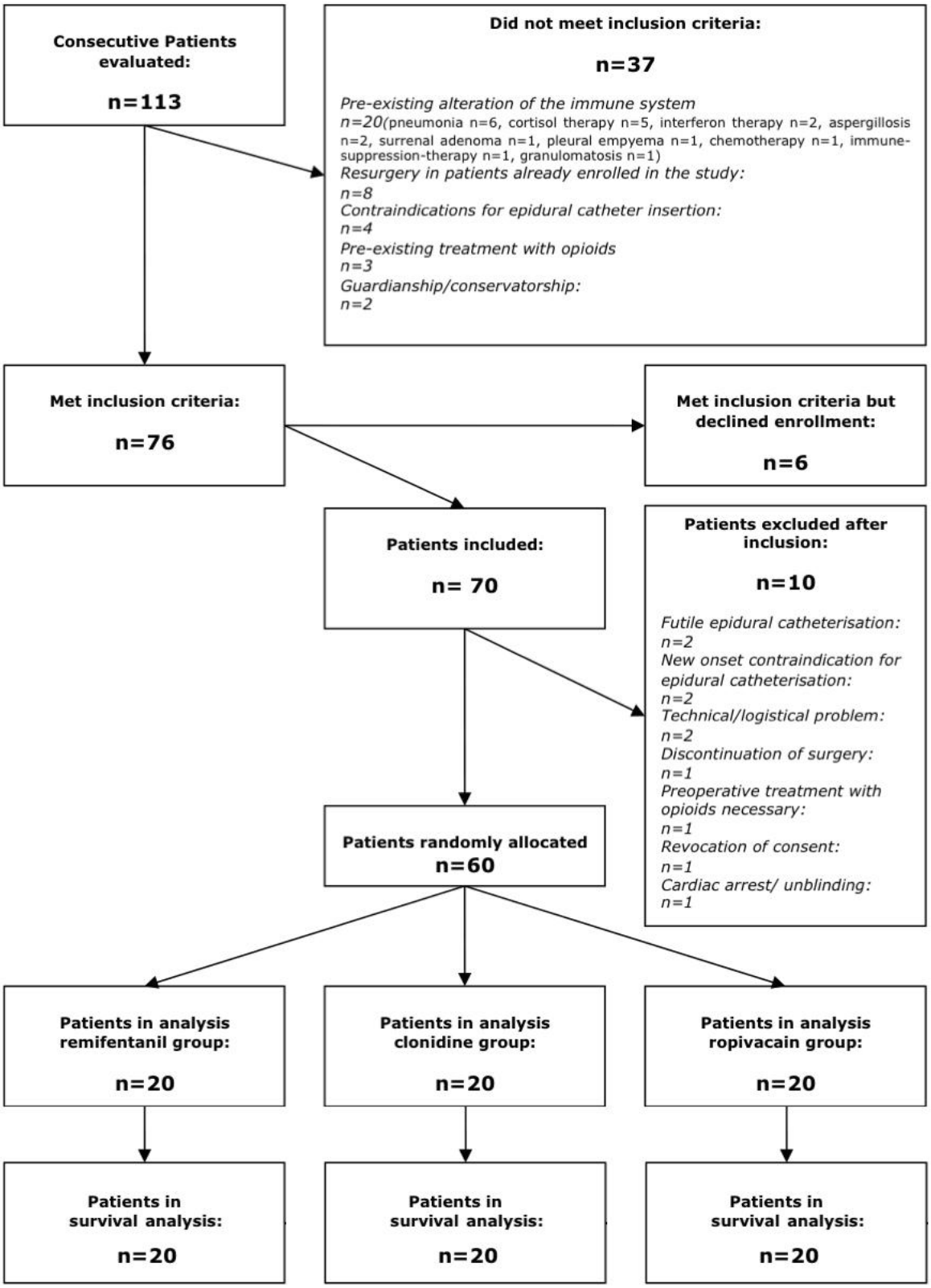

Figure 2. Flow of participants

“Flow Chart showing the process of selection and randomization to treatment with remifentanil, clonidine or ropivacaine of the lung resection surgery patients who were included in the study (data presented according to the Consolidated Standards of Reporting Trials [CONSORT] guidelines(55). n = Sample size”(9) (permission granted)

“A total of 113 consecutive patients were screened from January 2006 to May 2007 and 60 patients met the inclusion criteria and were finally randomized into three groups to be treated with remifentanil, remifentanil plus clonidine or ropivacaine. According to the CONSORT guidelines, the flow of participants is shown in Figure 2. “(9)

4.2 Basic Characteristics of the Study Patients

“There were no statistically significant differences between the groups in the measured demographic characteristics.”(9)

Basic Characteristics	**Remifentanil Group**; **n=20**	**Clonidine Group; n=20**	**Ropivacaine Group**; **n=20**	**P Value**
Age, yr	66.5 (50.0-70.5)	66.5 (61.0-73.0)	65.5 (63.0-70.5)	0.79
BMI, kg/m2	26.3 (21.5-29.7)	27.1 (24.0-30.4)	26.5 (22.1-30.0)	0.65
Sex (F/M)	7 (35%)/ 13 (65%)	9 (45%)/ 11 (55%)	4 (20%)/ 16 (80%)	0.23
ASA classification I/ II/ III/ IV. No	0/ 8/ 12/ 0	0/ 11/ 9/ 0	0/ 8/ 12/ 0	0.54
Current smoking, No.	3 (15%)	9 (45%)	7 (35%)	0.10
Preoperative FEV1, L	2.45 (1.98-3.33)	2.43 (1.93-2.71)	2.67 (1.53-3.31)	0.82
Coexisting cardiovascular disease, No.	11 (55%)	14 (70%)	14 (70%)	0.52
Pre-existing beta-blocker therapy, No.	7 (35%)	5 (25%)	8 (40%)	0,58
Pre-existing antidiabetic therapy, No.	3 (15%)	4 (20%)	3 (15%)	0.88

Table 2. Demographic and clinical characteristics of the trial groups

“Data are presented as median (quartiles 25-75) or numbers (frequency in %). All parameters were taken on admission to the hospital. No. = number”(9) (permission granted)

4.3 Clinical Characteristics of the Study Patients

“There were no statistically significant differences between the groups in the measured clinical or hemodynamic characteristics. Operating time, heart rate, systolic and diastolic blood pressure before and after induction of anesthesia, oxygenation indices under one lung ventilation, VATS rates and cancer incidence did not significantly differ between the groups (Table 3). 76% of the patients underwent lung resection via the lateral thoracotomy approach; the remaining 24% underwent VATS. None of the patients developed early-onset pneumonia or any other postoperative infection within the first three postoperative days. There were no differences between the groups in any clinical endpoint (Table 4). Perioperative pain was assessed using the NRS (numerical rating scale) at rest and during coughing. There were no differences between the groups in NRS scores.”(9)

	Remifentanil Group (n=20)	Clonidine Group (n=20)	Ropivacaine Group (n=20)	P Value
VATS, No.	6 (30%)	5 (25%)	3 (15%)	0.50
Cancer histologically confirmed, No.	14 (78%)	16 (80%)	17 (85%)	0.65
Operating time, minutes	142.5 (90.0-236.25)	157.0 (90.0-213.7)	132.0 (80.0-178.7)	0.81
Oxygenation index before OLV	344.7 (296.4-384.0)	366.6 (309.2-411.6)	365.9 (335.8-400.3)	0.57
Oxygenation index after 20 min of OLV	175.5 (87.4-260.0)	115.3 (83.5-235.8)	168.0 (118.0-281.0)	0.28
Oxygenation index at lung resection	258.0 (166.1-319.0)	173.4 (87.6-236.7)	271.2 (119.0-321.0)	0.10
Heart rate difference, BPM	28.5 (25.0-35.0)	25.0 (20.0-35.7)	25.0 (20.0-30.7)	0.24
Heart rate before induction, BPM	81.0 (70.5-87.2)	73.5 (65.0-80.0)	70.0 (65.0-81.5)	0.08
Heart rate at lung resection, BPM	70.0 (64.5-80.0)	63.5 (56.2-77.2)	62.0 (55.0-80.0)	0.39
Systolic BP before induction, mmHg	132.5 (128.5-158.7)	130.0 (122.0-153.7)	130.0 (120.0-145.7)	0.53
Diastolic BP before induction, mmHg	75.0 (70.0-80.0)	75.5 (62.2-80.0)	72.5 (61.2-80.0)	0.55
Systolic BP at lung resection, mmHg	110.0 (100.7-127.5)	115.0 (96.2-130.0)	110.0 (103.0-115.0)	0.73
Diastolic BP at lung resection, mmHg	62.0 (60.0-70.0)	60.0 (50.0-70.0)	65.0 (57.0-70.0)	0.39

Table 3. Clinical characteristics and hemodynamic parameters

“Data presented as median (25 - 75% quartiles) or *n* or *n* (%).

No statistically significant between-group differences (*P* > 0.05; Kruskal–Wallis test or χ2-test).

Heart rate difference was assessed as the difference between maximum and minimum heart rate. OLV = One lung ventilation; min = Minutes; BPM = Beats per minute; BP = Blood pressure; mmHg = millimeter of mercury”(9) (permission granted)

Clinical Endpoints	Remifentanil Group (n=20)	Clonidine Group (n=20)	Ropivacaine Group (n=20)	P Value
Pneumonia, No.	0	0	0	-
Pneumothorax, No.	12 (60%)	10 (50%)	11 (55%)	0.95
Resurgery, No.	2 (10%)	1 (5%)	1 (5%)	0.77
Transfused patients, No.	3 (15%)	3 (15%)	1 (5%)	0.47
Patients admitted to ICU, No.	12 (60%)	13 (65%)	13 (65%)	0.94
ICU stay, d	1.0 (0.0-1.0)	1.0 (0.0-1.0)	1.0 (0.0-1.7)	0.97
Readmission to ICU, No.	2 (10%)	2 (10%)	1 (5%)	0.78
Hospital stay, d	9.0 (5.0-10.7)	7.0 (5.0-12.0)	9.0 (5.0-12.7)	0.81
Death, No.	0	0	0	-

Table 4. Clinical outcomes

“Data presented as median (25 - 75% quartiles) or *n* (%).

No statistically significant between-group differences (*P* > 0.05; χ2-test). d = Days”(9) (permission granted)

4.4 The Intervention and Long-Term Survival

The return of the measurement of postoperative survival time was exceptionally high with no missing values. The measurement of the data was very precise with every data point being narrowed down to the day of death. It was therefore not necessary to censor any data within the period under consideration. Censoring is usually necessary due to the fact that no information about the event is available, and it weakens the validity of the statistical model because assumptions have to be made about all time spans between censoring and the end of the investigated period. For statistical analysis, all surviving patients were censored at the end of the analyzed period, i.e. survival times of patients who are still alive are termed censored survival times.

The statistical analysis was conducted per protocol because the majority of patients who were excluded didn’t receive any study medication while the reasons for exclusion

do not make a bias through exclusion plausible and because neither crossover nor compliance was an issue.

Because of the overall survival rate of 63.3%, the median of overall survival can only lie after the end of the observation period, and therefore it cannot be calculated. The same reasoning applies to the median of the survival within the therapy arms.

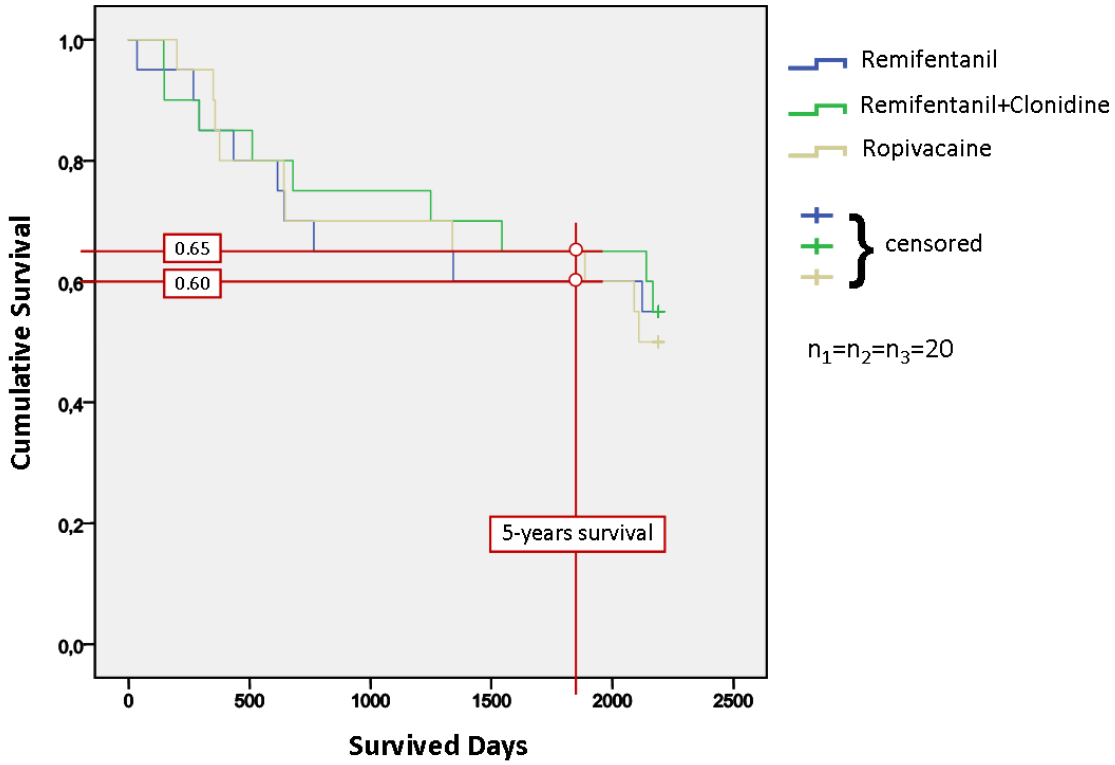

Figure 3. Kaplan-Meier curve

The graph of the Kaplan-Meier estimate is shown in Figure 3. The five-year survival rates (with standard error) in the three groups were 65% ± 10.7% for ropivacaine vs. 60% ± 11.0% for remifentanil vs. 65% ± 10.7% for remifentanil plus clonidine, favoring no therapy over the other. Accordingly, the test statistic for the Log-Rank test is 0.154 (p=0.926), for the Breslow test 0.161 (p=0.923) and for the Tarone-Ware test 0.158 (p=0.924).

With the Grambsch test being significant in this case (p=0.041), the condition of proportional hazard is not fulfilled.(56) Therefore, the test results have to be regarded

with caution, even though the test statistics besides the Log-Rank test (Breslow and Tarone-Ware) are robust against violations of proportional hazard and show similar results.

A power analysis (see Table 5) was performed for the Log-Rank test in the given situation which yielded a power of 5%. In order to reach a power of 80%, 1499 patients per therapy arm would be needed.

	Power needed	Power reached
Test significance level, α	0,050	0,050
1 or 2 sided test?	2	2
Group 1 proportion π_1 at time t	0,450	0,450
Group 2 proportion π_2 at time t	0,500	0,500
Hazard ratio, h=ln(π_1) / ln(π_2)	1,152	1,152
Power (%)	80	5
n per group	1499	20
Total number of events required, E	1568	21

Table 5. Log-rank test of survival in two groups followed for fixed time, constant hazard ratio

In order to test whether the survival rates (proportions) in the three groups are equivalent, a test of equivalence was performed.(57)

The difference of proportions between the groups (when the groups with no difference of proportions, namely ropivacaine vs. remifentanil and clonidine were chosen) was tested with specified confidence bounds of -0.2 and 0.2, respectively (wider confidence bounds would not be reasonable). The observed confidence bounds of -0.29 and 0.29, respectively, exceeded the specified confidence bounds, not rejecting the null hypothesis of non-equivalence. The one-sided p-value to reject non-equivalence is 0.139, also resulting in no rejection of the null hypothesis.

When the confidence bounds were chosen to be narrower with -0.1 and 0.1, respectively, the one-sided p-value to reject non-equivalence increased to 0.321. When the groups with a difference of proportions were tested (namely remifentanil vs. ropivacaine or alternatively remifentanil and clonidine vs. ropivacaine) with specified

confidence bounds of -0.2 and 0.2, respectively, the lower observed confidence bound rose to -0.341 (compared to -0.29 before). The one-sided p-value to reject non-equivalence was 0.220 (compared to 0.139 before). When the confidence bounds were chosen to be narrower with -0.1 and 0.1, respectively, the one-sided p-value to reject non-equivalence further increased to 0.439.

A second power analysis, this time to determine the number of patients needed in order to prove equivalence of groups instead of a difference between groups, was performed which yielded a power of 35% for an equivalence limit of 0.2 (15% for an equivalence limit of 0.1, respectively) when the standard proportion (π_S) of 0.45 or 0.50 and a test significance level α (one-sided) of 0.05 was chosen. A reduction of the test significance level α (one-sided) to 0.025 reduced the power to 24% (and to 9%, respectively).

In order to reach a power of 80%, at least 77 patients per therapy arm would be needed for an equivalence limit of 0.2. This number increases with a narrower equivalence limit of 0.1 (307 patients per therapy arm), with a reduction of the test significance level α to 0.025 (98 patients per therapy arm) or with both a narrower equivalence limit and a reduced test level (389 patients per therapy arm). These numbers are calculated for the standard proportion π_S being 0.45, with a diminutive change for a π_S being 0.50.
The test of equivalence refers only to the proportions of deaths at the end of the observation period, not to the chronological sequence of the patient's deaths. Therefore, the condition of proportional hazard does not have to be fulfilled for the test of equivalence.

4.5 The Predictors and Long-Term Survival

The factors that were measured as possible predictors had few missing values. Due to the univariate analysis any missing values of one factor didn't compromise the analysis of any other factors. The results are shown in Table 6. As previously mentioned, the Cox regression is connected with some requirements: First of all, the precondition of proportional hazard, which is not fulfilled. Therefore, results have to be regarded with reasonable caution. Secondly the number of influencing factors has to be limited, leading to altogether two covariates with 28 events in our case). Nevertheless, these results are shown in Table 7.

Predictor	Reference	Hazard Ratio	95% CI	P Value	n
Sex	Male vs. female	0.666	0.285 - 1.559	0.349	60
Age	Per additional year	1.058	1.005 - 1.115	0.033	60
BMI	Per additional unit	1.026	0.932 - 1.130	0.598	59
ASA	III vs. II	2.514	0.983 - 6.433	0.054	60
VATS	Open vs. VATS	0.590	0.240 - 1.450	0.251	60
Smoking	History vs. no history	1.261	0.427 - 3.726	0.675	60
FeV1	Per additional liter	0.681	0.405 - 1.143	0.146	53
Cancer	Cancer vs. no cancer	1.998	0.465 - 8.585	0.352	56

Table 6. Predictors with their hazard ratios, calculated with univariate Cox regression.

Predictor	Reference	Hazard Ratio	95% CI	P Value	n
Sex	Male vs. female	0.648	0.269 - 1.562	0.334	60
Age	Per additional year	1.060	1.006 - 1.116	0.028	60
BMI	Per additional unit	1.031	0.935 - 1.137	0.543	59
ASA	III vs. II	2.585	0.993 - 6.729	0.052	60
VATS	Open vs. VATS	0.600	0.241 - 1.494	0.273	60
Smoking	History vs. no history	1.314	0.438 - 3.938	0.626	60
FeV1	Per additional liter	0.639	0.373 - 1.095	0.103	53
Cancer	Cancer vs. no cancer	2.053	0.475 - 8.864	0.335	56

Table 7. Predictors with their hazard ratios, calculated with bivariate Cox regression in order to adjust for the intervention group.

Because of the borderline p-value of around 0.05 for ASA, its large clinical effect, its practical applicability as a risk factor and its routine use, an additional Kaplan-Meier curve of the two ASA groups is shown in Figure 4.

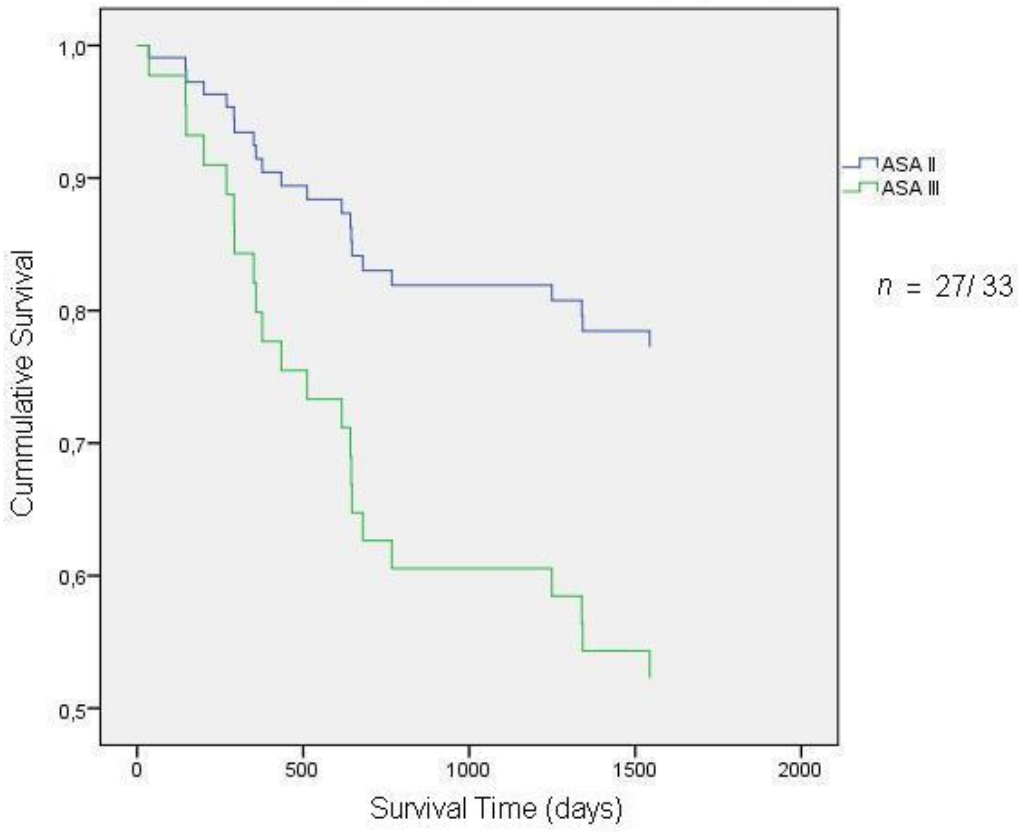

Figure 4. Kaplan-Meier curve: ASA as a predictor of long-term survival

Despite of the permitted number of only two covariates, we included - though with critical assessment by the reader in mind – more covariates into the Cox regression showing enlarged p-values for the three most promising predictors (age 0.033 → 0.215; ASA 0.054 → 0.278; FeV1 0.146 → 0.560) with hazard ratios tending to 1 (age 1.058 → 1.040; ASA 2.514 → 1.720; FeV1 0.681 → 0.846). Similar results can be calculated without the therapy arm as a covariate with the following p-values (age 0.028 enlarged to 0.233; ASA 0.052 enlarged to 0.463; FeV1 0.103 enlarged to 0.442) and hazard ratios (age 1.060 → 1.039 ; ASA 2.585 → 1.472; FeV1 0.639 → 0.789).

One reason for this is the correlation between the predictors, which is highly significant between age and FeV1 (p = 0.001), significant between age and ASA (p = 0.021) and not significant between ASA and FeV1 (p = 0.109) with the correlation coefficients being 0.439 for age ~ FeV1, 0.265 for age ~ ASA and 0.172 for ASA ~ FeV1 (calculated with Spearman-Rho, one-sided).

When the observation period is changed, the estimates and the p-values of the three most promising predictors change as well (Table 8).

	365 (d)	730 (d)	1096 (d)	1461 (d)	1826 (d)	2192 (d)
Age estimate of risk	1.172	1.069	1.069	1.054	1.058	1.043
Age p-value	**0.011**	**0.039**	**0.033**	**0.048**	**0.033**	**0.048**
ASA estimate of risk	2.945	2.162	2.263	2.332	2.514	3.116
ASA p-value	0.178	0.148	0.103	0.080	0.054	**0.010**
FeV1 estimate of risk	0.852	0.637	0.663	0.681	0.681	0.568
FeV1 p-value	0.685	0.138	0.158	0.146	0.146	**0.021**

Table 8. Age, ASA and Fev1 as predictors in the context of various lengths of observation periods (univariate Cox regression with the previously described references and sample sizes)

5 Discussion

5.1 Postoperative Survival Time

In adult patients without severe cardiovascular or any immunological disease who undergo any thoracoscopic or open lung resection, the analgesia during lung resection in the form of epidural ropivacaine in comparison to intravenous remifentanil in comparison to intravenous remifentanil in combination with intravenous clonidine does not have an effect on long-term survival which is measurable in small sample sizes.

5.1.1 Comparison with Other Studies

In order to compare the results with those of other studies, a literature search with PubMed using the key words “epidural survival lung surgery” was performed in June of 2015. It showed no other study which aimed to determine the influence of intraoperative epidural anesthesia on long-term survival in patients who undergo lung surgery. However, a wide range of studies investigated similar or related questions, even though the randomized controlled trials are clearly in the minority. The exact search syntax reads as follows:

epidural[All Fields] AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms]) AND ("pulmonary surgical procedures"[MeSH Terms] OR ("pulmonary"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "pulmonary surgical procedures"[All Fields] OR ("lung"[All Fields] AND "surgery"[All Fields]) OR "lung surgery"[All Fields])

Altogether PubMed showed 203 items. Out of those, 63 items were at least in some way linked to the topic of this study. Out of those, 29 items were relevant enough to compare them with the present study in terms of study design, type of patients, intervention, outcome and number of patients. An overview of those 29 items is shown in Table 9. Out of those 29 items, a few studies which display similarities to the present study or which reveal other noteworthy contributions to the associated topics are described in the following.

No.	Author	Patients	Intervention	Outcome	Study Design	n
1	Powell ES	L: pneumonectomy	EA vs paravertebral block	major comp	prosp. multicen.	312
2	Lluch M	L: single lung transplantation	-	cardiopulmonary parameters	retros. monocen.	8
3	Liu SS	CABG	GA vs GA+EA vs GA+SPA	myocardial infarction, mt	meta-analysis	1178
4	Muehling B	infrarenal aneurysm repair	GA vs GA+EA/ fast track	mb, mt, LOS, ILOS	R	101
5	Licker M	L: pneumonectomy	GA vs GA+EA	respiratory comp	retros. multicen.	193
6	Powell ES	L: pneumonectomy	EA vs paravertebral block	major comp	prosp. multicen.	312
7	Lehman JF	colon surgery	SA vs EA	LOS, peristalsis	retros.	102
8	Ammar AD	abdominal aortic surgery	PCA vs PCEA	comp	retros. monocen.	80
9	Major CP jr.	abdominal aortic surgery	SA vs PCEA	pulmonary comp, mt	retros.	65
10	Bauer C.	L: lobectomy	GA vs GA+EA	lung function, pain	R	68
11	Cerfolio RJ	L: lung resection	-	mb, mt	retros.	85
12	Wisner DH	rib fractures, elderly	SA vs EA	pulmonary comp, mt	retros.	307
13	Lawrence VA	noncardiothoracic surgery	-	pulmonary comp	review	
14	Licker M	abdominal aortic surgery	SA vs EA vs ITM	extubation, mb, mt	retros.	595
15	Palermo S	L: lung surgery	SA vs EA	analgesic effect	R	50
16	Wu CL	surgery	SA vs EA	mb, mt	retros.	12780
17	Rivers SP	infrainguinal arterial reconstruction	GA vs EA	comp, mt, LOS	prosp. monocen.	213
18	Tenenbein PK	cardiac surgery	GA vs GA+EA	pulmonary function	R	50
19	Muehling BH	L: lung surgery	GA vs GA+EA/ fast track	respiratory comp, mb, mt	R	55/59 (ITT)
20	van Lier F	major abdominal surgery (with COPD)	GA vs GA+EA	pneumonia, mt	retros. cohort	541
21	Dumans-Nizard V	L: lobectomy/ wedge resection	GA vs GA+EA/ fast track	mt, LOS, feasibility	prosp. monocen.	100
22	Wijeysundera DN	noncardiac surgery	SA vs EA	mt	retros. monocen. (matched pairs)	259037/ 88188
23	Kopeika U	L: lung surgery	SA vs EA	comp, pulmonary function	prosp. monocen.	453
24	Wu CL	L: segmental excision	SA vs EA	mb, mt	retros. cohort	3501
25	Almakadma YS	esophagectomy	-	mt, ILOS	retros.	45
26	Amat-Santos IJ	transapical transcatheter aortic valve implantation	EA vs ICC	pain, comp, mt	prosp.	135
27	Edwards MS	abdominal aortic aneurysm (endovascular)	GA vs EA vs SPA vs LA/ MAC	complications, mt, LOS	retros.	6009
28	Svircevic V	cardiac surgery	GA vs GA+EA	comp, mt	R	654
29	Cata JP	L: lung resection (cancer)	PCEA vs PCA vs PCEA+PCA	mt (recurrence-free/ overall)	retros.	445

Table 9. Results of the literature research

L: = lung surgery; CABG = coronary artery bypass graft; EA = epidural analgesia; GA = general anesthesia; SPA = spinal anesthesia; SA = systemic analgesia; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; ITM = intrathecal morphine; ICC = intercostal catheter; comp = complication; mt = mortality; mb = morbidity; LOS = length of stay; ILOS = length of stay in intensive care; R = randomized controlled trial; prosp. = prospective; retros. = retrospective; multicen. = multicenter; monocen. = monocenter; ITT = intention-to-treat analysis

Altogether, only six of the 29 items are randomized trials, which illustrates the general deficit of relevant data about the topic. 12 items specifically examine patients who undergo lung surgery, but only three of those are randomized trials, with the other three randomized trials examining patients who undergo surgery of the circulatory system. Out of the studies among the 29 items only eight compare general anesthesia with general anesthesia in combination with epidural anesthesia. At least 18 studies defined mortality (with any observation period) as one of the outcomes, with a strong emphasis on 30-day mortality.

Muehling et al. describes a prospective randomized trial that compares general anesthesia with general anesthesia in combination with epidural anesthesia (as part of a fast track recovery program), but does so examining patients who undergo elective open infrarenal aneurysm repair.(58) The fast track regime includes the lack of bowel preparation, reduced preoperative fasting, patient-controlled epidural anesthesia, enhanced postoperative feeding and postoperative mobilization. It was not feasible to blind; in order to reduce the resultant bias, objective criteria of patient management were set. The trial aimed at morbidity, mortality (30d), length of stay in the intensive care unit, length of stay and the need for postoperative mechanical ventilation. No deaths occurred during the observation period, and while the number of patients with medical complications was significantly lower in the fast track group, this is due to the difference in functional bowel obstruction, which is both a consequence of the sympatholysis and opiate reduction through the epidural block as well as the other interventions of the fast track regime that also improve bowel function.

Bauer et al. and Palermo et al. both conducted randomized trials with patients undergoing lung surgery, and while the epidural block was tested as intervention, mortality wasn’t among the outcomes. In the study of Bauer et al. patients of the control group received no epidural anesthesia during or after surgery, which resulted in an enhanced pulmonary function and better pain relief in the intervention group. Even though it was not the aim of the study, the in-hospital mortality was described to be not significantly different between the groups.(59) In the study of Palermo et al. the difference between intervention and control groups consisted only in the postoperative analgesia, showing a higher efficacy of the epidural anesthesia.(60)

Powell ES et al. undertook a multicentre, prospective, observational cohort study in 2005 in order to assess the short term risks after pneumonectomy (due to lung cancer), listing age, ASA ≥ 3, preoperative diffusing capacity for carbon monoxide and epidural anesthesia as the strongest risk factors for major complications.(61)(62) However, the validity of these results suffers from limitations of the study design such as the lack of randomization or blinding and poorly chosen outcome parameters like “unplanned intensive care admissions” and “inotrope usage” instead of infections or organ failures, which would be far better to define the occurrence of a major complication. Most of the patients (61.1%) received epidural anesthesia while the main alternative was paravertebral block (31%), which is often used when there are contraindications for epidural anesthesia. Therefore, the study design allows for unequal assessment of ICU admissions: A patient who presents with a contraindication for epidural anesthesia (due to preexisting diseases) might postoperatively be admitted to the ICU in a planned manner, while a healthier patient without any contraindications might postoperatively be admitted to the ICU in an unplanned manner, which creates an - entirely formal - “major complication” regarding the latter patient even though the health status of the latter patient might be better than that of the first patient, and even though both receive intensive care. The study has been criticized for further shortcomings, without any response from the authors.(63) In any case, it compares different variations of regional anesthesia which doesn’t contribute to answer the hypotheses raised in the present study.

Epidural anesthesia has been tested with respect to various outcomes in other forms of surgery(64)(65)(66).

5.1.2 The Patients

The patients in this study who had to undergo lung surgery showed the perioperative biphasic sequence of initial proinflammation and subsequent anti-inflammatory counterregulation. Additionally, a group difference could be shown, “indicating less inflammatory stimulation during surgery”.(9) This group difference did not translate into a measurable difference in long-term survival.

Comparing studies when the patients, the kind of surgery, local mortality rates or therapy standards differ can result in a misleading meta-analysis when applicability is considered.(67)

5.1.3 The Intervention

Table 9 shows how different studies examine different applications of epidural anesthesia. Some try to find effects only in the intraoperative phase, while others solely focus on postoperative recovery. Bauer et al. managed to design a study where analgesia differs both intra- and postoperatively without the ethical problem of an epidurally placed sham catheter.(59)

In clinical practice, some anesthetists use the epidural catheter from the very beginning of the operation (as was the case also in the present study), while others start the application of local anesthetics midway through surgery or towards the end of it. So applicability and comparability is subject to differences between and among studies and clinical standards.

Neurogenic blocks can interfere with a vast array of physiological and pathophysiological processes. While surgical trauma, stress and pain influence the immune system and the immune system influences cancer cells, cancer cells themselves also influence the immune system, while neurogenic blocks can interfere with all of these interdependencies.

Das et al. summed up the knowledge about these effects in his paper “Are we causing the recurrence - impact of perioperative period on long-term cancer prognosis: Review of current evidence and practice”:(68)
“Although complex and controversial, morphine seems to exert its tumor promoting effects via:
1. Promotes apoptosis in lymphocytes and macrophages by activation of the enzymes involved in apoptotic cell death.
2. Affects NO release and inhibits cell adhesion.
3. Decreases the intracellular concentrations of cyclic adenosine monophosphate (AMP)

4. Inhibits binding of NF-kB.
5. Increases angiogenesis by activating cyclooxygenase(COX)-2, reciprocal transactivation of VEGF receptors, and production of prostaglandin (PG)-E2.
6. Stimulates tumor cell migration and proliferation *in vitro*.(69)
7. Suppresses NK cell cytotoxicity.
8. Promotes tumor metastasis and invasion by increased secretion of urokinase like plasminogen activator.(70)”(68)

Regarding the central α2-agonist clonidine he notes:
“Certain tumor cell lines express α2 adrenoceptors on their surface. Stimulation of the receptor by agonists (clonidine, dexmedetomedine) was shown to stimulate proliferation of tumor cells on top of their NK cell modulating activity.”(68)

And the multiple pathways of inhibition of tumor cells that are known to be caused by local anesthetics are gathered as follows:
“The possible mechanisms may be:
1. Alteration of DNA methylation of cancer cells.
2. Reactivation of tumor suppressor genes.
3. Direct cytotoxic effect.
4. Direct inhibitory effect on the epidermal growth factor (EGF) receptor.
5. Reduced mesenchymal stem cell proliferation.

Regional anesthesia *per se* can attenuate cancer recurrence by several mechanisms:
1. Decreased neuroendocrine stress response of surgery as indicated by the suppression of the rise in serum cortisol level.
2. Reduced need for general anesthesia.
3. Reduced opioid consumption.
4. Maintains NK cell, lymphocyte, and monocyte activity.
5. Perioperative pain management is superior when regional anesthesia is performed.“(68)

There is some evidence that local anesthetics can reduce the rate of recurrence in melanoma,(71) breast cancer,(72) prostate cancer(73) and tongue cancer,(74) and anesthetic techniques are a relevant factor.(75)

5.1.4 The Outcome

The Kapaln Meier graph (Figure 3) shows an informative profile of the postoperative years, with a constant die off during the first 700 days, followed by a sudden change to a reduced mortality rate which is also constant for another 1100 days, followed by an increase in the mortality rate, the nature of which remaining unknown due to the lack of further data. There seem to be two phases in the first five postoperative years, and they seem to be associated with different hazards. The first two years seem to show a proportional hazard and might be an adequate time span for further studies. When one compares the results of this study with other publications a lack of randomized controlled trials that measure long-term survival is obvious.

Amat-Santos et al. conducted a prospective study of the effect of TEB in comparison with ICC on clinical outcomes following transapical transcatheter aortic valve implantation.(76) Among the clinical outcomes was one-year mortality. Even though the TEB-group had a lower baseline left ventricular ejection fraction, the overall one-year mortality rate was higher in the non-TEB-group (31.1%) than in the TEB group (10.8%), with $p = 0.005$. As the trial was not randomized, a propensity score-matched analysis was undertaken in order to reduce selection bias, yielding TEB as an independent predictor of decreased cumulative late mortality in a multivariate Cox regression.

5.1.5 Limitations

The lack of postoperative infections or perioperative death is a sign not only of the inclusion criteria, but also of the high quality of the medical care of all disciplines involved. The literature shows a rather different picture of the scale of morbidity and mortality that is accepted in the perioperative period of lung surgery, e.g. the incidence of postoperative pulmonary complications being 10% to 37%.(77) The high quality of medical care in the present study is both highly desirable for the patient as well as undesirable for the measurement of a difference between groups, because morbidity and mortality rates are low.(17)

While other studies show a 4- to 10-fold increase in the incidence of hypotension when epidural local anesthetics were compared to systemic opioids,(11) such an effect was absent in the present study (as can be seen from Table 3).

Additionally any study may produce a Hawthorne effect which increases the quality of the diagnostics and therapy of study patients.(78) Study patients are generally known to have a better outcome when compared to the basic population.(79) In that sense quality not only makes for less noise in the data and therefore improved discernability, but also for less unwanted complications and therefore reduced discernability.

Another problem that has two facets in a similar way can be identified: The limitation of the length of the three therapy arms. On the one hand, it would have been unethical to place a sham epidural catheter with the sole purpose of a successful blinding during the study, with little or no net benefit for the patient (though it can be argued that epidural saline might have an effect,(80) that the patient profits from the placebo effect and that study patients generally have better outcomes). On the other hand, a prolonged intervention with both an intraoperative as well as postoperative difference in therapy might have a more pronounced effect on all parameters that were measured. Here the novel approach of Bauer et al. could be promising,(59) but it too has its drawbacks and is not feasible for everyone.

One limitation that has already been extensively discussed is the low power of this study. A follow-up study with higher numbers of participants could remove any doubt whether differences between the groups might be so small that they can only be registered by using large numbers of participants.

5.1.6 Statistical Methods

The results of the statistical tests prove that neither a difference of the risk of dying during the five years after lung surgery nor an equivalence of the risk to have died at the end of the five year period can be shown with the present study with respect to the three therapy arms. The test for equivalence is a hint that this might be the case due to the low power of the study, and the power needed to prove equivalence is markedly lower

than the one needed to prove a difference. The equivalence of the risk of dying during the five years after lung surgery could not be tested as no suitable method is available.

In summary it can be concluded that either the difference is relatively small or that there is no real difference.

Additionally one can deduce that the statistically significant immunological modulation that differs between the therapy arms does not translate into either a measurable difference in infections or long-term survival, at least with the power of this study.

5.1.7 Negative Findings

Negative results are usually not favoured in the scientific community, as they offer two very different interpretations: Either the methods were faulty so that the noise due to mistakes blur the difference between two groups or that the methods were sound but that there really is no difference between the two groups. The former is useless, as in this case no knowledge is gained. The latter is a useful finding, as in this case it shows us which hypotheses have already been tested and don't need to be tested again (at least not under the same conditions - here method development, study design and furthermore the utilization in meta analyses come into play), therefore saving resources for the extensive and laborious testing of other, new hypotheses that might produce positive test results.

“I have not failed. I’ve just found 10,000 ways that won’t work.”
Thomas Edison (1847-1931)

The problem with negative results is that they can't be useful if there is no way to discern between the two cases outlined above. In the clinical trial, which is the basis of this study, the very nuanced differences between the groups regarding the perioperative immune modulation as well as the predictors for long-term survival have shown that noise due to faulty methods is not the problem, as otherwise noise would have drowned out any of the already measured nuanced differences.(9)

Unfortunately, a culture of publication bias affects both of the aforementioned possible cases of why negative results occur, leading to less publication even of believable - and therefore useful - negative results.

In this whole context, the feasibility of large randomized controlled clinical trials itself must be questioned.(81)(82) However, not only the statistical problem of a sufficiently large sample with correspondent power, but also the rising financial and administrative burden of a randomized controlled trial impedes their realization, favoring studies by the biased pharmaceutical industry which is far less restricted in its financial and administrative means but partial in its profit motive.(83) This is regrettable, and even though the scientific community often laments the lack of hard evidence that is provided mainly by large and independent randomized controlled trials, the described developments are unlikely to be reversed any time soon.

5.1.8 Applicability

Because of the randomization of the patients and therefore the absence of a selection bias, a statistically significant result would prove causality, even though this is limited by the fact that the present study is not the primary objective of the clinical trial. The statistical proof of a difference would contribute to the growing field of oncoanesthesia,(68) while the statistical proof of equivalence would contribute to the discussion about the gold standard for lung surgery. This very discussion has been substantially affected by the recent meta-analysis on the impact of epidural analgesia on mortality and morbidity after surgery by Pöpping et al.(12), which “has shown that the preponderance of evidence demonstrates that postoperative epidural analgesia not only provides “soft” benefits such as early mobilization and reduction in venous thromboembolism but also affords a survival advantage that is meaningful, given the large numbers of eligible patients.”(11)

This significance is further specified:
“The strength of the benefit varied from a statistically significant 40% decrease in odds of death to a borderline significant 25%, depending on the studies included, and the number needed to treat to prevent a death ranged from about 55 to 250.”(11)

Of course the kind of studies that were included have a strong influence on the transferability on the present study. But beyond that, the number needed to treat 55 to 250 patients shows how our study with 60 patients and no death within in the first month is underpowered to show a difference in the early postoperative mortality of the therapy arms. The first study patient died after 35 days, followed by the time spans of 146 and 148 days for the second and third study patients.

The problem of detectability of an effect by small studies of high quality is brought up as well:
“Controversy remains regarding the effect of epidural analgesia on mortality, with large database studies suggesting a 30-day mortality benefit {[odds ratio (OR) = 0.89; 95% confidence interval (CI), 0.81–0.98] and [OR = 0.74; 95% CI, 0.63–0.89]} whereas smaller, higher quality randomized controlled trials such as the MASTER trial (N = 915) and the Veterans Affairs study (N = 1021) showing no difference, likely because of the large sample size needed to detect a mortality difference.”(11)

Nevertheless, the relevance of even small risk reductions is valued accurately:
“Finally, despite the small absolute risk reduction (ie, 3%–2%), the findings are still clinically important because of the very large population of patients to whom the results apply.”(11)

The time span for which mortality should be registered is also considered:
“The majority of benefit was realized in the 30- to 60-day range, a biologically plausible outcome due to the cumulative benefits on individual organ morbidity.”(11)
Here a distinction should be made between various effects: The direct postoperative complications with short-term consequences (e.g. pneumonia), the direct postoperative complications with long-term consequences (e.g. some thromboembolic events) and the complications at a later date with long-term consequences (e.g. cancer recurrence). The additional death rate through aging, accidents, the underlying disease and other primarily unrelated illnesses can be attenuated as a source of interference through randomization, but nevertheless these effects have also to be considered when interpreting short-term and long-term postoperative mortality.

Summing up it can be said that even though to date no one has aimed at the same goal as the present study, the results nevertheless complement the previous state of knowledge.

5.2 The Predictors

The predictor “sex” was not significant after univariate analysis or with correction for the intervention. It should be mentioned that women were clearly in the minority and that gender-specific differences in smoking habits and other aspects of lifestyle might play a role, along with many other factors.

The predictor “age” was significant both after univariate analysis and with correction for the intervention, and this is valid not only for the observation period of five years, but for any observation period between one and six years. Its ability to predict is even stronger in short observation periods, showing the biggest estimated additional risk in combination with high significance during the first year. This implies that age is more relevant for the prediction of survival after an operation than it is for the general prediction of the remaining life expectancy. It shows a lot of overlap with other measurable factors, including the other two predictors which are significant after six years, namely ASA and FeV1. An aspect in its favor is its effortless measurement. It is primarily a formal, not a functional attribute.

The predictor “BMI” was not significant after univariate analysis or with correction for the intervention. It is generally a poor concept, as it does not differentiate between different tissues (mainly fat tissue, muscle tissue, water and bones) that make up the human body. An apt example is the BMI of a bodybuilder which can easily reach values that are equal to those of another person that is already limited in his or her movement by excessive fat tissue. Therefore, any methods that measure the actual percentage and distribution of body fat are more suitable. There is however an exception, because a very low BMI shows a lack of tissue, with little range of variation for the remaining tissue. Here, much more meaningful findings exist.(84) BMI is also primarily a formal, not a functional attribute.

The predictor “ASA” was significant both after univariate analysis and with correction for the intervention, but only after an observation period of six years, showing only marginal significance - and therefore only weak evidence for an effect - after five years. Its ability to predict is even weaker in short observation periods, showing smaller estimated additional risks - though with no significance - when applied during the first 365, 720, 1096 or 1461 days. This implies that it is more relevant for the prediction of the remaining life expectancy, rather than the prediction of survival after an operation. It shows a lot of overlap with other measurable factors, including the other significant predictors. An aspect in its favor is its effortless measurement, as it is routinely assigned by the assessing anesthetist. An additional advantage is that it is a functional, not a formal attribute and that it reduces complexity, expressing the general fitness and health status in only one number. It should be noted that the sample consisted exclusively of patients with ASA II and III. This is an adequate reflection of the respective population as patients with ASA I neither have the typical risk factors such as lung disease and nicotine abuse nor do they show serious symptoms which would bring about a detection of a lung disease that needs to be operated on. Patients with ASA IV usually won’t have the suitable prognosis or physical resources to qualify for a lung operation with one lung ventilation.

The predictor “VATS” was not significant after univariate analysis or with correction for the intervention. It should be mentioned that VATS were the distinct minority. Nevertheless one would expect a pronounced difference due to the summation of many factors such as severity of the underlying disease, tumor size, tissue trauma and other complications that are associated with open resection.

The predictor “smoking” was not significant after univariate analysis or with correction for the intervention. It should be mentioned that patients without a history of smoking were the distinct minority. If speculations about causality are made, it is questionable whether patients without a history of smoking have the same chance of survival as patients with a history of smoking. Rather, all patients without a history of smoking that have to undergo lung surgery may be so sick that their chances of survival even approach those of the patients with a history of smoking. Another reasoning would be to once again make the distinction between formal and functional parameters, with the history of smoking being a formal one.

The predictor “FeV1” was significant both after univariate analysis and with correction for the intervention, but only after an observation period of six years. Its ability to predict is weaker in short observation periods, showing smaller estimated additional risks - though with no significance - when applied during the first 365, 720, 1096 or 1461 days. This implies that it is more relevant for the prediction of the remaining life expectancy, rather than the prediction of survival after an operation. In contrast to the other predictors, this parameter has seven missing values, making a significant result less likely. Nevertheless, the estimated additional risk of death during the six years after surgery is reduced to 57% for one additional liter of FeV1 (p-Value = 0.021). It shows a lot of overlap with other measurable factors, including the other significant predictors. The objective measurement of obstruction requires some effort, but this doesn’t impair its role as a practical predictor, as it is routinely performed because of the underlying disease or as part of the common preoperative assessment. It is a functional, not a formal attribute.

The predictor “cancer” was not significant after univariate analysis or with correction for the intervention. The four missing values are unlikely to be the decisive factor for this. It should be mentioned that patients without cancer were the distinct minority. Nevertheless one would expect a pronounced difference due to the summation of many factors which are associated with cancer. But one could argue that patient who have to undergo lung surgery suffer from other conditions that are similarly compromising their health. And one could consider the fact that lung surgery was considered only as a curative option (i.e. no debulking) - probably curing most of the patients through the operation and filtering out those severe cases where curative surgery is no longer an option.

In summary, there is not enough evidence that those predictors that measure or represent function are superior to merely formal ones, but the only exception to this rule was age. Being a formal predictor, it shows a 17% elevated additional risk (of death within the first postoperative year) for each year of one’s life with a p-value of 0.011.

ASA, FeV1 and age are accessible, reliable and significant predictors of postoperative survival, though it is a requirement when using both ASA and FeV1 to choose the right

observation period. All three predictors are superior to the other predictors which mostly show plausible estimates of additional risk but lack significance.

The published opinion that a predictor should be rejected only because more comprehensive or suitable ones could be developed or because they were initially not designed to be a predictor is unfounded.(85)

5.3 Conclusion

While intraoperative thoracic epidural block decreases the IFN-γ/ IL-4 ratio immediately after lung surgery, an influence on long-term survival could not be shown. This is most likely due to the high NNT (number needed to treat) that has been shown in meta-analyses, making further randomized controlled trials with higher numbers of patients necessary.

Meaningful predictors for reduced long-term survival could be identified, confirming age and ASA as common tools for preoperative assessment.

6 Abbreviations

α	test significance level
ADHD	attention deficit hyperactivity disorder
AND	Boolean operator
ASA	American Society of Anesthesiologists (physical status classification system)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BS	blood sample
BW	body weight
CABG	coronary artery bypass graft
CDC	Centers for Disease Control and Prevention
cm	centimeter
comp	complication
CONSORT	Consolidated Standards of Reporting Trials
CPAP	continuous positive airway pressure
CRF	case report form
CRO	contract research organization
CT scan	X-ray computed tomography
d	days
EA	epidural analgesia
ECG	electrocardiography
EudraCT	European Union Drug Regulating Authorities Clinical Trials database
FeV1	forced expiratory volume in one second
GA	general anesthesia
GCP	good clinical practice
h	hour
ICC	intercostal catheter
ICU	intensive care unit
IFN-γ	Interferon gamma
IL-4	Interleukin 4
ILOS	length of stay in the intensive care unit
ISRCTN	International Standard Randomised Controlled Trial Number register
ITM	intrathecal morphine
ITT	intention-to-treat analysis
kg	kilogram
KKS Charité	Koordinierungszentrum Klinische Studien Charité

L	liters
L:	lung surgery
LOS	length of stay
mb	morbidity
µg	microgram
mg	milligram
min	minutes
ml	milliliter
mmHg	millimeter of mercury
monocen.	monocenter
mt	mortality
multicen.	multicenter
n	sample size
NITS	non-intubated thoracic surgery
NNT	number needed to treat
No.	number
NRS	numerical rating scale
NSCLC	non-small-cell lung cancer
NYHA	New York Heart Association
OLV	one lung ventilation
OR	Boolean operator
p	p-value
PACU	post anesthesia care unit
PCA	patient-controlled analgesia
PCEA	patient-controlled epidural anesthesia
prosp.	prospective
π_S	standard proportion
R	randomized controlled trial
retros.	retrospective
SA	systemic analgesia
SCLC	small-cell lung cancer
SD	standard deviation
SPA	spinal anesthesia
TEB	thoracic epidural block
Th	thoracic vertebra
TNM	tumor, nodes, metastases
VATS	video assisted thoracoscopic surgery

7 Tables and Figures

8 Literature

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Diese Arbeit ist Robert Barth gewidmet. Ruhe in Frieden.

10 CURRICULUM VITAE – Markus Renius

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

11 Publikationsliste von Markus Renius

Publikation 1: Markus Renius, Edoardo Viviano, Jens-C. Rückert, Angelika Bloch, Christian Meisel, Anja Harbeck-Seu, Willehad Boemke, Mario Hensel, Klaus-D. Wernecke und Claudia Spies

„Wirkung der thorakalen Epiduralanästhesie, sowie von Remifentanil und Clonidin auf den Schmerz und die perioperative Immunantwort von Patienten, die lungenreseziert werden“

Veröffentlicht als Poster auf dem 12. HAI 2010 - Der Hauptstadtkongress der DGAI für Anästhesiologie und Intensivtherapie (Berlin)

(Posterpreis für klinische Studien)

Publikation 2: Edoardo Viviano, Markus Renius, Jens-C. Rückert, Angelika Bloch, Christian Meisel, Anja Harbeck-Seu, Willehad Boemke, Mario Hensel, Klaus-D. Wernecke und Claudia Spies

„Selective neurogenic blockades and perioperative immune reactivity in patients undergoing lung resection”

Veröffentlicht als Poster auf dem Euroanaesthesia 2010 (Helsinki)

Publikation 3: Edoardo Viviano, Markus Renius, Jens-C. Rückert, Angelika Bloch, Christian Meisel, Anja Harbeck-Seu, Willehad Boemke, Mario Hensel, Klaus-D. Wernecke und Claudia Spies

„Selective neurogenic blockades and perioperative immune reactivity in patients undergoing lung resection”

Veröffentlicht als Poster auf dem ISICEM 2010 (Brüssel)

Publikation 4: Edoardo Viviano[1], Markus Renius[1], Jens-C. Rückert, Angelika Bloch, Christian Meisel, Anja Harbeck-Seu, Willehad Boemke, Mario Hensel, Klaus-D. Wernecke und Claudia Spies

[1]) Geteilte Erstautorenschaft

„Selective neurogenic blockades and perioperative immune reactivity in patients undergoing lung resection“

Veröffentlicht in “The Journal of International Medical Research”, 2012

Publikation 5: Johannes Kurth, Gunnar Lachmann, Markus Renius, Klaus-D. Wernecke und Claudia Spies

"Influence of an immunomodulatory treatment on Th17 cells, regulatory T-cells and the occurrence of infectious diseases in patients with immunodeficiency: a randomized controlled trial"

Veröffentlicht als Vortrag auf dem 14. HAI 2012 - Der Hauptstadtkongress der DGAI für Anästhesiologie und Intensivtherapie (Berlin)

Publikation 6: Anton Goldmann[1], Markus Renius[1], Christin Zachmann, Robin Kleinwächter, Clarissa von Haefen, Klaus-D. Wernecke, Claudia Spies

[1]) Geteilte Erstautorenschaft

Influence of preoperative vaccination on monocytic HLA-DR expression and postoperative infection rate of patients with upper aerodigestive tract cancer: A randomised trial.

Veröffentlicht in „European Journal of Anaesthesiology“, 2015

Publikation 7: Alawi Lütz, Gunnar Lachmann, Markus Renius, Clarissa von Haefen, Klaus-D. Wernecke, Marcus Bahra, Alexander Schiemann, Marco Paupers, Christian Meisel, Claudia Spies

"Influence of Granulocyte-Macrophage Colony-stimulating Factor or influenza vaccination on HLA-DR, infection and delirium days in immunosuppressed surgical patients: double blind, randomised controlled trial"

Veröffentlicht in PLoS One (Public Library of Science), 2015

12 Eidesstattliche Versicherung

„Ich, Markus Renius, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: "Influence of selective neurogenic blocks on long-term survival of patients undergoing lung resection" selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE/ www.icmje.org*)* kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o.) und werden von mir verantwortet.

Meine Anteile an Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit der Betreuerin angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

13 Anteilserklärung an erfolgten Publikationen

Markus Renius hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Edoardo Viviano[1], Markus Renius[1], Jens-C. Rückert, Angelika Bloch, Christian Meisel, Anja Harbeck-Seu, Willehad Boemke, Mario Hensel, Klaus-D. Wernecke und Claudia Spies

[1]) Geteilte Erstautorenschaft

„Selective neurogenic blockades and perioperative immune reactivity in patients undergoing lung resection“

Veröffentlicht in “The Journal of International Medical Research”, 2012

Beitrag im Einzelnen:
Prüfarzt mit umfangreicher Beteiligung an
Planung (Organisation von Abläufen und Zusammenarbeit aller Schnittstellen wie Labore, Doktoranden, Pathologie, Intensivstation, Station, etc.),
Patientenrekrutierung (Screening und Einschluß),
Patientenbetreuung (prä-, intra- und postoperativ),
Datenerhebung (einschließlich der Eingabe in die Datenbank und der Plausibilitätskontrollen),
Laboranalysen (ConA-Stimulation, Präparation und Inkubation der Proben),
Safety (Detektion der AEs und SAEs),
statistischer Analyse (deskriptive Analyse),
Interpretation,
Ausformulierung des publizierten Textes,
Korrektur des publizierten Textes,
Zustimmung zur Veröffentlichung

Publikation 2: Markus Renius, Edoardo Viviano, Jens-C. Rückert, Angelika Bloch, Christian Meisel, Anja Harbeck-Seu, Willehad Boemke, Mario Hensel, Klaus-D. Wernecke und Claudia Spies

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Unterschrift des Doktoranden