DOCTORAL THESIS

INTERVENTIONAL BRONCHOSCOPY IN TREATMENT OF LUNG CANCER

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1. PREFACE

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1.2 SUMMARY

BACKGROUND: Lung cancer remains one of the most frequent and lethal forms of cancer in the world. Many of these patients experience airway obstruction and its complications. Interventional bronchoscopy can be a useful tool in palliative treatment, and even be a curative option in certain types of malignant lung disease.

AIMS AND METHODS: This doctoral work was performed at the Intervention Centre, Oslo University Hospital, Rikshospitalet in close collaboration with The Department of Respiratory Medicine, Oslo University Hospital, Rikshospitalet. The project had an aim to collect, systematize and analyze our institutional experience. As a part of this aim, our research group assessed survival, complications and anesthesiology challenges in patients with different types of airway obstruction and different histological types of cancer after bronchoscopic treatment, evaluated effectiveness of interventional bronchoscopy in the treatment of carcinoid tumors, and evaluated the impact of palliative bronchoscopic procedures on quality of life, dyspnea score and lung function in lung cancer patients.

Four papers were included into this thesis. They consisted of three retrospective studies (Paper I, II and IV) and one prospective study (Paper III).

RESULTS: In Paper I our group reported and analyzed the experience of interventional bronchoscopy with regard to complications and survival in 257 patients with central airway obstruction due to malignant disease. The study showed that median survival following interventional bronchoscopy was 15 weeks. No difference was found between survival times in the primary and the metastatic lung cancer groups (15 and 18 weeks respectively, $p = 0.25$), whereas survival time in patients with small was significantly lower 7 ($p = 0.04$). Serious complications such as bleeding, pneumothorax or obstruction during the procedure were rare (2.3%).

The study in Paper II included 73 patients with bronchial carcinoids, where 48 were treated with surgical resection and 25 with laser ablation. The study showed that among 25 patients treated endoscopically, 16 were successfully treated with laser, whereas 9 of the patients underwent surgery subsequently. There was no significant difference in survival between the two groups (p=0.9). None of the 69 survivors had any sign of recurrence on CT scans and bronchoscopy by the end of the study.

In Paper III the impact of interventional bronchoscopy treatment on quality of life, dyspnea and lung function was evaluated in 15 cancer patients with airway obstruction with malignant airway obstruction. The study showed that bronchoscopic treatment had a persistent effect on quality of life and dyspnea that remained 2 months after procedure. The study population had also a significant improvement in lung function after bronchoscopic treatment.

Ventilation and anesthesia experience in the period 1999-2012 was reported and discussed in Paper IV. Among 561 patients treated with 902 endoscopic procedures, 60 procedures were performed cases of critical airway stenosis. In these procedures one could see more frequent use of laryngeal mask airway (21.7 %), change of airway device (33%) and a higher complication rate (4.3% vs. 29.9%). Median long-term survival in lung cancer patients with or without critical airway obstruction was 100 and 182 days after procedure respectively. However, there was no significant difference in short-term (90 days) survival probability between the groups (0.65 and 0.51 respectively, p=0.14).

CONCLUSIONS: Bronchoscopic treatment is a safe option and complications are rare. Laser treatment may be offered as a standalone procedure in curative treatment of typical carcinoid tumors in the central airways, in selected patients. The data indicate positive impact of interventional bronchoscopic treatment on quality of life, dyspnea scale values and lung function in patients with advanced lung cancer and airway obstruction. Multidisciplinary team approach is important.

1.3 LIST OF PAPERS

PAPER I

Survival and Complications Following Interventional Bronchoscopy in Malignant Central Airway Obstruction: a Single Centre Experience*.* Neyman, Kirill; Sundset, Arve; Espinoza, Andreas; Kongerud, Johny; Fosse, Erik. *J Bronchol Intervent Pulmonol, Volume 18, Number 3, July 2011*

PAPER II

Endoscopic Treatment of Bronchial Carcinoids in Comparison to Surgical Resection: A Retrospective Study. Neyman, Kirill; Sundset, Arve; Naalsund, Anne; Espinoza, Andreas; Solberg, Steinar; Kongerud, Johny; Fosse, Erik. *J Bronchol Intervent Pulmonol, Volume 19, Number 1, January 2012*

PAPER III

Changes in Quality of Life, Dyspnea Scores, and Lung Function in Lung Cancer Patients With Airway Obstruction After a Therapeutic Bronchoscopy. Neumann, Kirill; Sundset, Arve; Espinoza, Andreas; Kongerud, Johny; Fosse, Erik. *J Bronchol Intervent Pulmonol, Volume 20(2):134-139, April 2013.*

PAPER IV

Critical Airway Obstruction: Challenges in Airway Management and Ventilation During Therapeutic Bronchoscopy. Andreas Espinoza, Kirill Neumann, Per Steinar Halvorsen, Arve Sundset, Johny Kongerud, Erik Fosse. *In Press J Bronchol Intervent Pulmonol, Volume 22, Number 1, January 2015*

1.4 ABBREVIATIONS

CO_2 – Carbon dioxide

CT – Computer Tomography

FEV1 – Forced Expiratory Capacity in 1 second

FVC – Forced Vital Capacity

FiO_2 - Fraction of Inspired Oxygen

Nd:YAG laser - Neodymium-doped Yttrium Aluminium Garnet laser

NSCLC - Non-Small Cell Lung Cancer

PEF – Peak Expiratory Flow

SCLC - Small Cell Lung Cancer

2. INTRODUCTION

2.1 Lung Cancer

2.1.1 Historical Note on Lung Cancer

Lung cancer is not a single neoplasm but a group of aggressive malignant tumors of the lower respiratory tract. The history of lung cancer starts with etiology and dates back to 1420, when the first mines were opened in Schneeberg (1). However, malignant disease of the lung was extremely rare in the early 1900's. For example, in a foreword to his book from 1912 named "Primary Malignant Growths of the Lungs and Bronchi: A Pathological and Clinical Study", the author rises a question if there is any point in writing a whole book on something that is "among the rarest forms of the disease"(2).

The early part of the epidemic in the beginning of the 20th century was associated with the typical 20 to 30-year lagging period between initiation of smoking during World War I and the actual tumor formation . An important breakthrough in understanding the etiology of lung cancer and appreciating its association with tobacco smoking was the paper on The British Doctors Study by Richard Doll and Austin Hill, confirming the suspicion that lung cancer was associated with smoking (3).

Public perception that patients with lung cancer are to blame for their disease, lack of awareness and poor patient advocacy were among the main causes of relatively poor funding in lung cancer research. However, the scientific and public interest to the problem has grown extensively within the last years and this will hopefully lead to a breakthrough in prevention, diagnosis and treatment of this disease.

2.1.2 Epidemiology of Lung Cancer

It is by far one of the most lethal of human tumors in the world (4). It is currently the second most common type of cancer in males after prostate cancer. In females it is the third most common cancer type after breast and uterine cancer (5;6). In Norway all cancer cases are thoroughly registered by the Cancer Register of Norway. According to their recent report, lung cancer was the second most frequent type after prostate cancer in men and third most frequent in women after breast and colorectal cancer.

Despite the advances in the diagnosis and treatment of lung cancer in the recent years, the overall 5-year survival rate still remains as low as 9-15% (5;7). Lung cancer was on the first place among causes of mortality in both genders, with 26,5 % in men and 17,9 % in women (8). Although five-year survival for lung cancer patients has not changed substantially over the last decades, a slight improvement during the recent years seems intriguing. This may be a result of better surgical treatment, earlier stage at presentation, and less co-morbidity.

2.1.3 Risk Factors

Extensive prospective epidemiologic data clearly establish cigarette smoking as the major cause of lung cancer (9;10). The lifetime risk of developing lung cancer among male and female smokers is 17% and 12% respectively, whereas this risk is significantly lower in nonsmokers, 1.3% in men and 1.4% in women respectively (11;12).

Cigarette smoke contains over 60 known carcinogens, including radioisotopes from the radon decay sequence, nitrosamine, and benzopyrene (13). The most famous smoke component nicotine is toxic and addictive, but it is not carcinogenic. However, it appears to depress the immune response to malignant growths in exposed tissue (14). Passive smoking is often a cause of lung cancer in nonsmokers (15).

Radon is considered to be the second most important cause of lung cancer after tobacco smoking (16-19). Exposure to asbestos, arsenic, nickel, radiation, and air pollution can also give an increased risk of developing lung cancer (20-23).

2.1.4 Symptoms and Diagnosis

Lung cancer is often associated with multiple symptoms, such as dyspnea, cough, haemoptysis, pain, and anorexia (24). Lung tissue has no pain innervation and a tumor may grow without giving symptoms over a long time. About 10% of all tumors are diagnosed accidentally and about 80% of lung cancer patients have an advanced metastatic disease at the time of diagnosis (25). Screening for lung cancer has been a controversial topic internationally (26;27). Chest X-ray and sputum cytology used earlier are nowadays more and more replaced by Chest Computed Tomography due to its higher sensitivity and specificity (28-32). However, studies show that screening should be limited only to smokers in the age of 55-75 years (33).

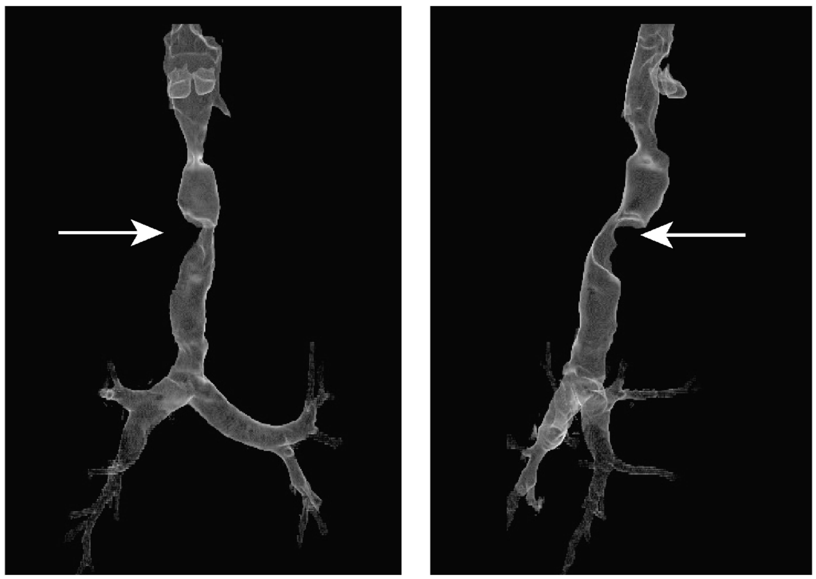

Figure 1. *Reconstruction of computer tomography of trachea in a patient with severe stridor and dyspnoea as debut symptoms of tracheal cancer. Anterior view in the left panel, and right lateral view in the right panel; the arrows pointing at the narrowest calibre which was measured to 2 mm.*

2.1.5 Histopathology

Histology of the tumor is crucial in treatment of lung cancer, and tissue samples should therefore be obtained whenever possible (34). Malignant tumors are classified into two major categories: small cell (SCLC) (15%) and non-small cell carcinomas (NSCLC) (80%). The non-small cell tumors are subdivided into three types (35-37): squamous cell (30%), adenocarcinoma (35%) , and large cell carcinoma (15%). The World Health Organization lung cancer classification (2004) can be presented in its short version as follows (38):

- Preinvasive lesions (dysplasia and cancer in situ)
- Small cell carcinoma
- Squamous cell carcinoma
- Adenocarcinoma
- Large cell carcinoma
- Adenosquamous carcinoma
- Carcinoid tumors (Typical and Atypical)
- Sarcomatoid Carcinomas
- Carcinomas of salivary gland type (Mucoepidermoid carcinoma; Adenoid cystic carcinoma; Epimyoepithelial carcinoma)

A full version of the histological classification is discussed elsewhere (39-41). A significant change in pathologic classification of adenocarcinoma was introduced after an expert publication in 2011. The new classification takes into consideration gene mutations in the tumor cells, which makes it possible to give the patients a more personalized chemotherapy treatment and opens new avenues for lung cancer research (42-48).

2.1.6 TNM Classification and Staging of Lung Cancer

The TNM Classification of Malignant Tumors is a cancer staging system that describes the extent of cancer in a patient's body. In this classification, the T part describes tumor size and whether it has invaded nearby tissue. The N part describes involvement of lymph nodes, both local and distant. The M part describes metastasis to other regions of the body. The full TNM classification was not included into this thesis. Its full version can be found elsewhere (49).

Based on the TNM Classification, one can define a stage of lung cancer. The stage of lung cancer is a description of the extent the cancer has spread, given in numbers I to IV with IV having the most progression. Staging of cancer is the most important predictor of survival, and cancer treatment is primarily determined by staging (49-51). Cancer staging can be divided into a clinical stage and a pathologic stage, that complement each other (52-55).

2.1.7 Treatment of Lung Cancer

Combined modality treatment is currently the method of choice in management of lung cancer, involving chemotherapy and radiation therapy with surgical treatment whenever possible (56). As it has been mentioned, lung malignancies can be divided into Small Cell Lung Carcinoma and Non-Small Cell Lung Carcinoma, and each of these two groups has different treatment susceptibility and prognosis, that would be shortly discussed hereunder.

Treatment of small cell lung carcinoma depends on whether the disease is limited or extensive(57). Multimodality treatment with curative intent is used in patients with limited stage of small cell carcinoma (58;59). Treatment of patients with extensive disease is barely palliative (60). Median survival in patients with limited disease is 10–18 months, and only 3–5 % seem to be totally cured. Median survival in patients with extensive disease is 6–10 months, and long-term recovery is rare (< 2 %) (61).

Patients with non-small cell carcinoma that are technically and medically operable should be offered surgical treatment (37;62). Patients with non-small cell lung carcinoma that are technically operable, but unfit surgery can be treated with high dose radiation, sometimes combined with chemotherapy (63-65). Recent advances in gene testing of adenocarcinoma samples with discovery of Epidermal Growth Factor Receptor (EGFR), Anaplastic

Lymphoma Kinase (ALK) and other tumor mutations has given a new perspective on treatment of this subgroup of lung malignancies (66-71).

2.2 Interventional Bronchoscopy

2.2.1 Historical Note on Interventional Bronchoscopy

In 1897, Gustav Killian was the first to report using a rigid bronchoscope to remove a piece of pork bone from a farmer's trachea (72). In the early years, the indications were removal of foreign bodies and dilation of strictures from inflammatory disease in the airways. The first flexible bronchoscope was developed as a diagnostic instrument by Dr. Shigeto Ikeda in 1960s, introducing the era of modern bronchoscopy (73). Improvement in anesthesia, illumination, and optical devices gave rise to the field of modern bronchoscopy with a burst of new diagnostic and treatment options in patients with almost any type of lung disease in both inpatient and ambulatory-care settings.

Interventional bronchoscopy has been introduced into the clinical practice since the 1980's, and has become truly widespread in the late 90s when their safety and efficiency was proved by the clinical studies. In Norway, Gunnar Hansen at the Aker University Hospital first introduced interventional bronchoscopy in the 1980's. In 1997 the interventional bronchoscopy activity and team were moved to the Department of Respiratory Medicine at the National Hospital of Norway (Rikshospitalet). At the Intervention Centre the procedures could be performed in an operation room designed for endoscopic procedures, providing better patient safety. A multidisciplinary team approach is used, involving anesthesiologists, interventional pulmonologists and dedicated operating room personnel.

2.2.2 Rigid and Flexible Bronchoscopy

Both rigid and flexible bronchoscopes are widely used in clinical practice. Rigid or open-tube bronchoscopes are hollow and have minimal airflow resistance, which makes it possible to ventilate the patient directly through them. Rigid bronchoscopes can be used to remove big tumors with physical effort or to remove foreign bodies or bronchial stents. They give good bleeding control, allowing to isolate the opposite lung from blood, to apply direct pressure at the bleeding spot and to insert various suction catheters while the patient remains ventilated. These properties make rigid bronchoscopes a superior safe instrument when a major bleeding occurs during procedure.

Flexible bronchoscopes are the instruments of choice in most of the diagnostic procedures. These bronchoscopes are typically easier to insert, much more comfortable for the patient and are associated with fewer complications. One can reach much smaller airways that that with a rigid bronchoscope, including upper lobe bronchi. However, flexible bronchoscopes are more expensive, easier to damage and have a smaller working channel of 2-2.5 mm in diameter. Furthermore, patients must breathe "around" the bronchoscope, which makes it difficult to maintain adequate ventilation in some cases.

2.2.3 Bronchoscopic Treatment Methods

Endoscopic treatment encompasses a broad range of therapeutic techniques, such as laser ablation, argon plasma coagulation, cryotherapy, photodynamic therapy, electocautery, balloon dilatation, stent insertion and many other (74-77). The choice of interventions is generally dictated by the patient's stability, the nature of the underlying problem, the overall prognosis, the particular expertise of the physician, and the available technology (78;79). In patients with large tumor masses, a rigid bronchoscope can be used for tumor debulking or silicone stent insertion. Lesions with endobronchial growth can be treated with ablation techniques, such as laser or cryotherapy. Extrinsic compression from tumors or enlarged lymph nodes can be treated with metallic or silicone stents. Mechanical dilatation of airways is a useful tool in both malignant and benign airway stenosis. A combination of different techniques can be used when required (80;81). Three main bronchoscopic techniques performed at Oslo University Hospital, and discussed in the thesis are shortly presented hereunder.

2.2.3.1 Bronchoscopic Laser Ablation

Laser (light amplification by stimulated emission of radiation) has three main properties: monochromaticity, collimation, and coherence. Laser light causes thermal, photodynamic, and electromagnetic changes in the living tissue, causing vaporization or coagulation with haemostasis. The Neodymium-doped Yttrium Aluminium Garnet (Nd-YAG) laser is often chosen for central airway obstruction. This laser has a wavelength of 1.064 mm. The power output can be adjusted from 5 to 100 W, with more coagulation effect at lower watts, whereas and vaporization of tissue can at higher watts. The vaporization of tissue is immediate, and the depth of tissue destruction can be up to 5 mm. This allows better coagulation and haemostasis of blood vessels during procedure. Complications reported in the literature include haemorrhage, perforation of a major blood vessel, endobronchial combustion, arrhythmias, myocardial infarction, and stroke (78).

2.2.3.2 Endobronchial Stents

Endobronchial stents are hollow tubular devices, made of silicone, metal wire, or a combination of those. The choice of the stent depends on whether it is malignant or benign disease. In malignant disease both metallic and non-metallic stents can be used. In benign disease, the silicone and hybrid stents are preferable, since metallic stents often cause a large amount of granulation tissue, which makes them difficult to remove at a later time point. Placement of the expandable metal stents can be performed with rigid or flexible bronchoscope, using fluoroscopy for placement guiding. The silicone stents do not collapse like the metal stents, and require therefore the rigid bronchoscope. Complications of endobronchial stenting include cough, pain, haemoptysis, migration, infection, obstruction with secretions or granulation tissue, erosion into the airway wall, and stent rupture (82).

2.2.3.3 Balloon Bronchoplasty

Balloon bronchoplasty is used for treatment of symptomatic airway stenosis. It can be performed as an independent procedure or as a precursor to airway stenting. Both flexible and rigid bronchoscopes can be used for this purpose. The balloon is filled with saline to a predefined pressure ranging from 6 to 15 atmospheres, applied for between 1 to 2 minutes, and repeated two to three times. Inflation diameter ranges from 4 to 20 mm, with a length of 4 to 8 cm. The final desired diameter is usually the normal diameter immediately proximal or distal to the stenosis. Complications are pain, re- stenosis, and airway rupture (83).

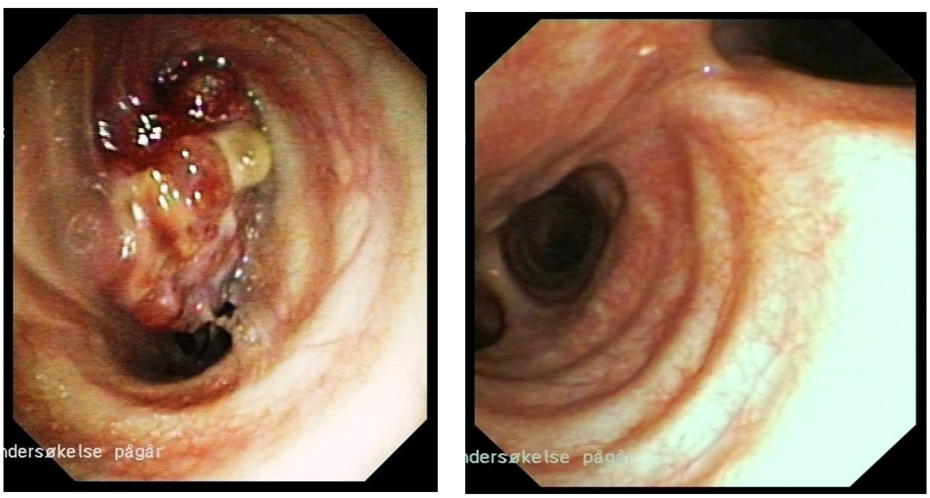

Figure 2. *An example of successful bronchoscopic laser eradication of endobronchial carcinoid. Picture to the left was taken under the first procedure, picture to the right was taken 1 year after the first procedure under control bronchoscopy.*

3. AIMS AND RESEARCH QUESTIONS

The aim of this doctoral work was to collect and systematize our institutional experience in interventional bronchoscopy since 1997 when it was introduced into clinical practice at the National Hospital of Norway (Rikshospitalet), Oslo University Hospital.

- Assessment of survival in patients with different types of airway obstruction and different histological types of cancer after bronchoscopic treatment (Paper I and IV)
- Evaluate effectiveness of interventional bronchoscopy in the treatment of carcinoid tumors of central airways compared to surgical treatment (Paper II)
- Evaluate the impact of palliative bronchoscopic procedures on quality of life, dyspnea score and lung function in lung cancer patients (Paper III)
- Assess complications after interventional bronchoscopy procedures at our institution (Paper I, II and IV)
- Assess anesthesiology and ventilation challenges connected to bronchoscopic procedures in patients with critical airway obstruction (Paper IV)

4. MATERIALS AND METHODS

4.1 Study design and population

Study I was a retrospective cohort study with 257 patients included. Study II was a retrospective cohort study on 73 patients. Study III was a prospective study with 15 participants. Study IV was a retrospective cohort study with 561 patients included.

All patients referred for interventional bronchoscopy were evaluated on the basis of medical history, clinical examination, a recent computed tomography of thorax, and bronchoscopy. Those patients assessed to have a life expectancy of >3 weeks, without severely compromised pulmonary circulation, and with patent airways distal to the stenosis, were accepted for treatment. Life expectancy assessment was based on the opinion of the referring pulmonologist or oncologist, and was discussed with one of the interventional pulmonologists. Patients were excluded if it was determined that conditions other than lung cancer could be responsible for the symptoms of dyspnea, haemoptysis, or chronic cough, or if the assessing interventional pulmonologist determined that the patient might be unable to tolerate bronchoscopy.

4.2 Endoscopic procedures

Most procedures were performed with a flexible bronchoscope through the endotracheal tube. In patients with large tumor masses, a rigid bronchoscope was used for tumor debulking or silicone stents insertion. Lesions with endobronchial growth were treated using laser or electrocautery. The laser was set to 40-45 W and one second laser followed by one second intervals to avoid tumor overheating and combustion. Extrinsic compression from tumors or enlarged lymph nodes was treated with metallic (Ultraflex) or silicone stents (Dumon, Hood). A combination of different techniques was used when required.

4.3 Anesthesia

The patients were anesthetized by total intravenous anesthesia, using propofol infusion (4-8 mg/kg/hr) and opioid intermittently or as infusion (remifentanil 0.1-0.5 μg/kg/min). Norcuronium or cisatracurium were used for induction of neuromuscular blockade. Repeated doses were administrated if prolonged neuromuscular blockade was needed.

The patients were ventilated by controlled ventilation using volume controlled mode. The choice of airway (orotracheal tube, laryngeal mask, or rigid bronchoscope) was made according to procedure and location of lesion. In patients with ventilation problems irrespective of chosen airway, manual ventilation was attempted before eventual change of airway. The proportion of oxygen in the anesthetic gas mix was 0.3-0.9 without using the laser and 0.35 ± 0.05 during laser ablation.

4.4 Data collection methods

In the retrospective studies both data from the departments database and medical charts was used. All the patients treated with interventional bronchoscopy methods were consecutively registered in the department's procedural database. Data from the database (patient demography, procedure type, disease category, problem codes, procedure duration) and supplemental information from patients medical charts (complications, nature of problem, attempted solution) for each procedure were collected and analyzed retrospectively. Information on the choice of airway (orotracheal tube, nasotracheal tube, tracheostomy cannula, laryngeal mask airway, rigid bronchoscope), and ventilation was collected from the database and medical charts.

Data for the prospective study was collected from medical charts and procedural database, as well as consequently during the study. All patients were followed up for 2 months by 4 assessments. The first assessment was performed 1 day before the procedure (T1); the second was performed on the day following treatment (T2), the third after 2 weeks (T3), and the fourth after 2 months (T4). The screening visit (T1) consisted of medical history, clinical assessment, and quality of life assessment using a questionnaire. Quality of life re-assessment using the questionnaire was performed at T3 and T4. The Borg Dyspnea Scale was used to assess each patient's intensity of dyspnea at baseline (T1) and 1 day after (T2) the interventional procedure. Lung function tests were performed at T1 and T2.

Survival after the first interventional bronchoscopy treatment was registered. Data from time of death in the studies was registered based on information from the National Population Registry of Norway.

4.5 Statistical analysis

Statistical analysis was carried out using SPSS program 18.0 (SPSS Inc., Chicago, IL). Survival time was estimated using Kaplan-Meier and Cox regression methods. The log-rank test was performed to compare results between the groups. The normal distribution of the variables was confirmed using Q-Q plots when applicable. A paired-samples t-test was used to compare these parameters. The non-parametric Wilcoxon test was used to compare results that were not normally distributed. A two tailed p-value <0.05 was considered as statistically significant.

4.6 Ethical considerations

The studies were approved by The Norwegian Regional Ethics Committee and the Norwegian Social- and Health Directorate. All participants in the prospective study gave their written consent before being enrolled.

5. RESULTS AND SUMMARY OF THE INDIVIDUAL PAPERS

PAPER I. Survival and Complications Following Interventional Bronchoscopy in Malignant Central Airway Obstruction: a Single Centre Experience.

In Paper I our group reported and analyzed the experience of interventional bronchoscopy with regard to complications and survival.

The data was collected on all our patients with central airway obstruction due to malignant disease (n=257), that were treated with endobronchial procedures during the period 1998-2009. The patients were grouped according to tumor type. Length of survival was compared between the groups. The patients with endobronchial carcinoid were excluded from the study. The results in these patients were analyzed separately (Paper II).

A) The study showed that median survival following interventional bronchoscopy was 15 weeks, and that eighteen patients died already within two weeks after the procedure. Survival in the primary and the metastatic lung cancer groups was 15 and 18 weeks respectively ($p = 0.25$). Survival in patients with small and non-small cell lung cancer was 7 and 17 weeks respectively ($p = 0.04$).

B) Serious complications such as bleeding (5), pneumothorax (1) or obstruction during the procedure (1) were rare (2.3%). All serious bleeding episodes occurred in patients with metastasis from renal carcinoma.

C) Sixty-seven patients (32%) were oxygen dependent at admission; 52 of them were discharged without oxygen. Four patients were on mechanical ventilation before the procedure; 3 of them were discharged after treatment.

D) Eighteen patients died within 2 weeks after the procedure. Eight of them were in danger of immediate suffocation, and were accepted for bronchoscopic intervention even though their life expectancy was limited. Ten patients died within the first 2 weeks after the procedure, even though their life expectancy had been preoperatively assessed as being longer than 3 weeks.

Conclusion: Life expectancy in patients with malignant airway obstruction was short and correlated to experience from other studies. Bronchoscopic treatment is a safe option and complications are rare.

PAPER II. Endoscopic Treatment of Bronchial Carcinoids in Comparison to Surgical Resection: A Retrospective Study.

Paper II was devoted to the results of endobronchial laser ablation in the treatment of bronchial carcinoid at our department. The outcomes were compared for the group treated with laser to the group that underwent surgical resection ("gold standard").

The study included 73 patients (29 men and 44 women, median age 53 years) with bronchial carcinoid. They were treated by surgical resection (n= 48) or endobronchial ablation (n= 25). Bronchoscopic treatment was also performed in 5 of the 48 surgical patients as part of the surgical treatment strategy.

A) The study showed that among 25 patients treated endoscopically, 16 were successfully treated with laser, whereas 9 of the patients underwent surgery subsequently. One major complication was registered, as an inadvertent ventilation with 100% oxygen caused a non-fatal fire of the flexible bronchoscope during Nd:YAG laser procedure.

B) Most of the 48 patients that underwent surgical treatment were operated with lobectomy and bilobectomy (30 and 5 patients respectively).

C) Four of the patients were dead by the end of the study, 1 treated with laser alone and 3 treated with surgical resection. Overall survival was 94.5% in the surgical group and 94.4% in the group treated with endoscopic ablation, showing no significant difference (p=0.9). None of the 69 survivors had any sign of recurrence on computer tomography and bronchoscopy by the end of the study.

Conclusions: Even though this is a retrospective study and no randomization has been performed, the results of the study add evidence to the view that endobronchial laser treatment may be offered as a safe, standalone procedure in treatment of typical carcinoid tumor in the central airways, in selected patients.

PAPER III. Changes in Quality of Life, Dyspnea Scores and Lung Function in Lung Cancer Patients with Airway Obstruction after Interventional Bronchoscopy Treatment

In Paper III the impact of interventional bronchoscopy treatment on quality of life, dyspnea and lung function in patients with malignant airway obstruction was evaluated.

This prospective study involved 15 cancer patients with airway obstruction that was treated with endoscopic procedures at our department. All patients gave their consent to participate and were followed up during 2 months by four assessments that consisted of a clinical examination, quality of life assessment using a Questionnaire, Borg Dyspnea Scale and Lung function tests.

A) The study showed that bronchoscopic treatment had a persistent effect on quality of life and dyspnea. This effect remained 2 months after procedure.

B) Improvement in fatigue scale was also significant, but not so persistent.

C) The study population had also a significant improvement in lung function after bronchoscopic treatment.

The data indicate positive impact of interventional bronchoscopic treatment on quality of life, dyspnea scale values and lung function in patients with advanced lung cancer and airway obstruction.

PAPER IV. Critical Airway Obstruction: Challenges in Airway Management and Ventilation During Therapeutic Bronchoscopy

Paper IV reports our experience with ventilatory management from 902 bronchoscopic procedures in 561 patients treated from 1999 to 2012. Challenges during these procedures, choice of the airway device and survival were discussed. Special attention was devoted to the patients with critical airway stenosis as ventilator management may be difficult in these cases compared to general lung cancer population.

Critical airway obstruction was defined as pre-procedural stridor, tracheal diameter <5mm, stenosis of both main bronchi, or with per-procedural clot/tumor fragments occluding trachea or both main bronchi. In total, 54 patients fulfilled these criteria (60 procedures performed).

A) The study showed that in patients with critical airway laryngeal mask airway was used more frequently than in general study population (21.7 % vs. 10.4% respectively).

B) One had to change the airway device in 20/60 procedures performed in patients with critical airway obstruction (33%). This is significantly higher than in patients without critical airway stenosis (55/842, 6%).

C) A higher complication rate was observed in the group with critical airway obstruction compared to the group without critical airway obstruction (29.9% vs. 4.3% respectively, $p<0.01$).

D) The survival for patients with malignant disease with or without critical airway obstruction was 100 (205) and 182 (592) days respectively, with 90 days survival probability of 0.65 and 0.51 ($p=0.14$).

Conclusion: In patients with critical airway obstruction change of airway during the procedure may be necessary according to operative requirements. Despite of this, the short-term survival is not different from lung cancer patients without critical airway obstruction.

6. DISCUSSION

6.1 DISCUSSION OF MATERIAL AND METHODS

This doctoral work is based on four studies performed at The National Hospital of Norway (Rikshospitalet), Oslo University Hospital, aiming to summarize our experience in interventional bronchoscopy. Some methodological considerations should be mentioned.

The first study was important for planning all of the other studies of the presented thesis. It was a retrospective study with a rather big number of participants (n=257). However, when divided into subgroups, the numbers were not always as impressive, for example in case with the small cell carcinoma patients (n=18). The small cell carcinoma patients in the study were highly selected. It is known that this type of lung malignancy usually responds well to chemotherapy and radiation therapy. Therefore, patients with recently diagnosed small cell carcinoma did not receive endoscopic interventions unless the situation was critical, and the patients were expected to die of suffocation before chemotherapy could be effective. A few selected patients with slow disease progression were also offered interventional procedures. A small number of patients in this group makes statistical analysis more vulnerable for statistical bias, limiting the conclusions that can be drawn from the study.

The second study was also retrospective, comparing laser ablation efficiency to surgical resection. All the patients treated with either of the modalities were included, and could therefore avoid selection bias. Number of patients was rather large for a study on bronchial carcinoids that are a rare type of lung malignancy. A prospective study addressing would have bees ideal, but randomization of these patients can be challenging. In the present study, carcinoids in the surgical resection group seem to involve the more distal airways or parenchyma than those in the laser treatment group. Therefore, the two subsets of patients are not exactly alike.

In the third paper of this thesis the impact of bronchoscopic treatment on lung function, dyspnea and quality of life in patients with airway obstruction due to malignant disease was assessed. In order to avoid selection bias, all patients that consented to participate were included based on the intention to treat principle. The study population was small and generalization from this study must be made with caution. Moreover, it is difficult to say whether the positive effect was only caused by endoscopic treatment, or whether it could be influenced by other types of therapy. However, it is known that a clinically meaningful improvement in quality of life can be rather difficult to achieve even with the use of other treatment modalities (84;85). One can conclude that at least the effect of bronchoscopic treatment one day after the procedure was not affected by other factors. Similar effects of bronchoscopic treatment were shown in a study by Amjadi et al (86).

Thorough objective testing of patients with advanced cancer and a short survival prognosis can be difficult. It turned out that many patients were not willing to participate in the study, either because they were exhausted after a long period of progressive disease with multiple diagnostic procedures, or because they understood the sinister prognosis and did not want to spend any of their time left filling out questionnaires. In critical discussions post factum our research group has come to a conclusion that a qualitative study might have been more feasible for this type of evaluation, and other researches that might be interested in performing a similar study can be recommended to consider this possibility. In general, this study should be considered as a pilot study, and a larger multi-centre study can be based on the results of the present work, taking into consideration the issues mentioned above.

The fourth study was retrospective as well and had a rather large number of patients included. The study was mostly descriptive in character, devoted to the ventilation challenges during bronchoscopic treatment. One of the limitations of the study was that the term "Ventilation problem" was defined quite loosely. If the operator or the anesthesiologist had experienced problems, this was accepted as "ventilation problem". This reflects the actual working conditions. In most of the patients undergoing interventional bronchoscopy some degree of desaturation or ventilation difficulty is experienced, but at some point the therapeutic team defines deterioration as a problem. That is really to be understood as "more of a problem than usual, and at the verge of changing operative strategy". This is far from a universal definition of "ventilation problem" but makes sense in small teams that are used to work together. The bronchoscopic team in the study consisted mainly of two interventional pulmonologists and two anesthetists, and a small group of nurses. Within such a group the concept of "ventilation problems" is meaningful, as there is a common experience and understanding of what this means. Also the definition of critical airway obstruction used in the study was mainly based on clinical presentation rather than a systematic classification (87). This is a typical limitation for almost any retrospective study as the information on the obstruction site, degree and type was not always available in all patient journals (88).

Prospective randomized controlled studies are to date a gold standard in assessment of the relation between exposure and outcome. It is however difficult to design a randomized controlled trial to determine the treatment strategies, since the well-established palliative effect of endobronchial treatment cannot be withheld from patients suffering from severe respiratory distress. Moreover, it would be unethical to randomize patients with obviously symptomatic airway obstruction, who require an immediate intervention, to a nonintervention arm. Neither it is possible to perform double-blinding in this group of patients. These challenges explain the lack of prospective studies on interventional bronchoscopy.

All of the studies in this thesis are single centre studies. Most of the current evidence supporting the use of interventional techniques has arisen from retrospective reviews and single-institution case series. However, the research on the field is shifting to randomized, controlled multicenter studies (89-91). This type of research would most likely improved interventional bronchoscopy position in the clinical practice. Despite the methodological limitations of this research work, our group believes that these studies represent a real-life situation that medical practitioners face in their clinical everyday life.

6.2 DISCUSSION OF MAIN RESULTS

6.2.1 Survival in different groups of lung cancer patients

One of the aims of the studies was to assess survival in different groups of lung cancer patients after interventional bronchoscopy treatment. Median survival in patients with primary and metastatic lung cancer at our institution was 15 weeks (110 days). This corresponds to data reported by some other authors (108 days in the study by Cavaliere et al. (92), 16 weeks in the study by Suh et al.(93)).

Short-time survival (90 days) in the patients with central airway obstruction due to malignant disease did not differ significantly from the patients without critical airway obstruction. Chhajed et al have shown that the survival of non-small cell lung carcinoma patients with malignant central airway obstruction, who received treatment with therapeutic bronchoscopy in combination with systemic chemotherapy with or without external beam radiation therapy, was similar to those who do not have critical airway obstruction and are treated only with systemic chemotherapy (94). This makes an important point that patients with advanced lung cancer with locally treated critical airway obstruction might have outcomes similar to those without critical airway obstruction, and should therefore be offered active treatment when possible.

The long-term survival in patients with critical airway obstruction was poorer compared to patients without critical airway obstruction. This probably reflects the disease being more advanced at the time of the first procedure. The influence of a single procedure on survival and the circumstances of death in an advanced disease are very difficult to assess.

Still, there is some evidence of its positive effect on general survival in the population with malignant airway disease. Eichenhorn et al demonstrated a longer median survival among those who underwent laser treatment and radiation therapy (340 days) compared with control subjects (198 to 266 days) after radiation therapy alone (95). The study of Brutinel et al showed a higher survival rate in patients treated with endobronchial laser compared with no treatment in the historical group (96). Shea et al found additional benefit when brachytherapy was administered with laser therapy (97). Furthermore, Razi et al have shown that timely airway stenting in patients with advanced lung cancer and airway obstruction gives better survival and significant cost savings with potentially considerable health care implications (98). Prevention or delay of airway obstruction complications such as post-obstructive pneumonia, sepsis, and respiratory failure certainly contribute to improvement in quality of life as well as survival (86). Such improvement in performance status can allow the patients to be considered for adjuvant systemic chemotherapy and/or external beam radiation as well as tissue sparing surgery when possible.

Metastatic lung disease is per definition a widespread disease and both physicians and patients alike may assume a poor prognosis. However, no significant difference in survival of these patients was found compared to the primary lung cancer group, and patients with metastatic lung disease should therefore be considered candidates for interventional endoscopic procedures.

In our material, 18 patients (6%) died within the first 2 weeks after the procedure. None of these early deaths was considered to be related to the interventional procedure. In a study of survival after stent insertion for malignant airway stenosis, Breitenbucher et al (99) reported a similar number of early deaths, as 3.5% of their patients did not survive the first week after stent insertion. In our 8 patients who died within 2 weeks, the interventional procedure was performed to avoid suffocation and was carried out even though their life expectancy was recognized as being limited. Disease severity was underestimated in some of the remaining 10 patients, but some of these early deaths were unexpected. This illustrates that the assessment of life expectancy is not simple in patients with malignancies and raises some ethical dilemmas about treatment of severely sick patients with cancer and respiratory distress.

Patients with critical airway obstruction have shown short-term outcomes similar to patients without critical airway obstruction. Chhajed et al. have shown that the survival of non-small cell lung carcinoma patients with critical airway obstruction , who received treatment with therapeutic bronchoscopy in combination with systemic chemotherapy with or without external beam radiation therapy was similar to those who do not have critical obstruction and are treated only with systemic chemotherapy (100)**.**

The influence of a single procedure on survival in an advanced disease is difficult to assess. Still, there is some evidence of its positive effect on general survival in the population with malignant airway disease. Eichenhorn et al. demonstrated a longer median survival among those who underwent laser treatment and radiation therapy compared with control subjects after radiation therapy alone (101). The study of Brutinel et al. showed a higher survival rate in patients treated with endobronchial laser compared with no treatment in the historical group(102), and yet other studies have demonstrated additional effect from laser therapy, or timely airway stenting on survival in lung cancer patients (103;104). Prevention or delay of malignant airway obstruction complications such as pneumonia, sepsis, and respiratory failure certainly contribute to the improvement in quality of life as well as survival (105).

6.2.2 Complications of interventional bronchoscopy

Another aim of this thesis was to assess the complication rate at our institution. Interventional bronchoscopy is known to be a safe tool with complication rate as little as 1% (0-2.2 %) in the hands of an experienced operator (78). In one of the largest existing studies on interventional bronchoscopy performed by Cavaliere et al. it was shown that complications of interventional bronchoscopy are rare – only 10 of 1000 patients in their study had serious hemorrhage (106). Numbers can differ from study to study depending on physicians experience and study population. However, this type of treatment has generally proved its safety and efficiency (86;107;108). The most common procedure-related challenges or complications during interventional bronchoscopy are hypoxia, hemorrhage and pneumothorax (109). Hypoxia is usually caused by low oxygen concentrations (<35 %) used to avoid burn injury during laser ablation and is mostly present in patients with serious respiratory failure. This is usually handled by oxygenation breaks in laser treatment (86;110).

In our practice serious complications were rare, and only one of them resulted in death of the patient. This patient with a highly vascularized lung metastasis from renal cancer in the right main bronchus also had a serious renal failure; he died of profuse bleeding in the airways during the 8th procedure. Endoscopic laser resection and mechanical debulking with rigid bronchoscope every 2 to three months prevented this patient from suffocation and prolonged his life for 1.5 years. In our material, literally all cases of serious bleeding occurred in patients with metastasis for renal carcinoma. Mechanical debulking of tumor masses should be avoided whenever possible in this group of patients.

Another serious complication was endobronchial combustion due to inadvertent high oxygen concentration (FiO_2 1.0) during laser treatment. This patient later suffered from recurrent episodes of airway infections and had to undergo repeated laser and balloon dilatation procedures to treat bronchial stenosis and scarring caused by combustion. After few procedures the patient improved, FEV1 increased to 70% predicted, and the airway infections subsided. It should be mentioned that this complication occurred short time after the bronchoscopic treatment was introduced at our institution.

Even though the complications might sometimes be serious, the patients with advanced lung cancer and airway obstruction, facing a death of suffocation, should be offered bronchoscopic treatment.

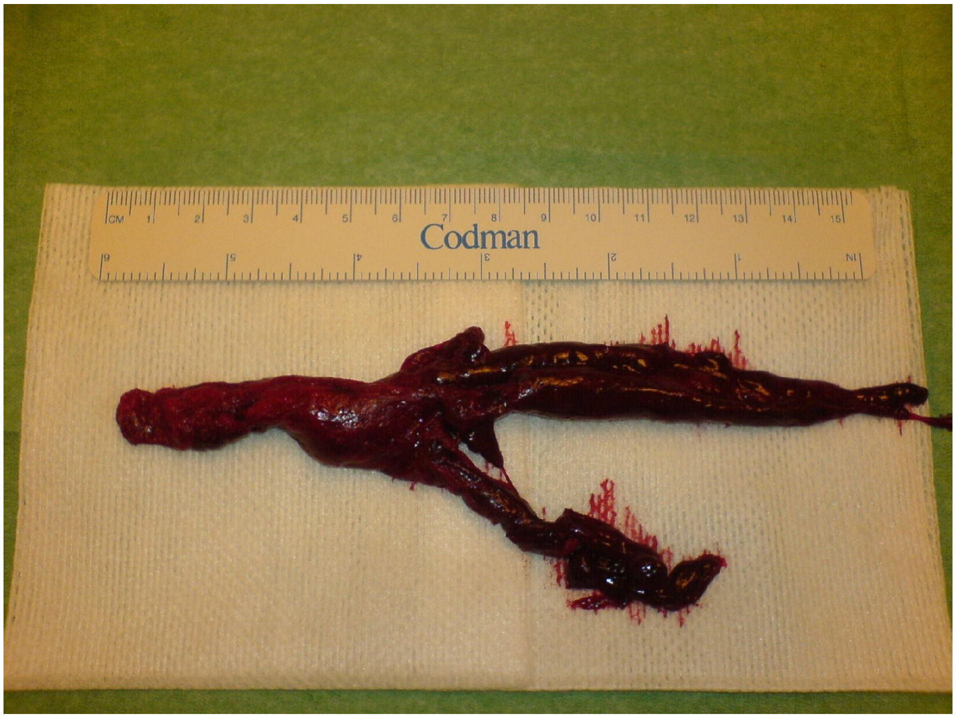

Figure 3. *Blood clot removed using rigid scope and forceps from the trachea in a patient with metastatic renal carcinoma in the right main bronchus. The clot occupied most of the lumen in the trachea and main bronchi. Due to profuse haemorrhage new clot obstructed the left main bronchus. The patient remained intubated in the intensive care unit over night, and the next day the clot was removed and the patient was extubated successfully. The patient survived 247 days after the procedure.*

6.2.3 Selection criteria for laser ablation in carcinoid patients

It was first shown in the study by Sutedja and co-workers that some patients had no recurrence of carcinoid after laser resection (111). Tendency for polypoid growth, central localization, low rate of local and distant metastasis, and high survival rate in patients with carcinoid tumors can suggest the bronchoscopic treatment to be an effective initial treatment alternative in a subset of the patients . However, patient selection remains challenging.

Several authors have proposed selection criteria for radical laser treatment (111-114). The most important of them could be distinction between intraluminal and extraluminal carcinoid tumors for selecting patients. A good bronchoscopic accessibility, typical carcinoid and no signs of extraluminal extension as well as no signs of metastases may also favor more reliable results of radical treatment (113). Patients with unclear tumor margin may be less suitable candidates for bronchoscopic treatment due to lower success rate in ablation. Atypical carcinoids have a much more aggressive behavior with higher metastasis rate and lower survival rate (115;116). There is no evidence regarding the effect of laser resection of atypical carcinoids, although some authors have reported good results of bronchoscopic treatment in these patients (117). In our opinion, patients with atypical carcinoids should be offered surgical resection.

Enlarged mediastinal lymph nodes may also exclude radical laser treatment (118). However, lymph nodes may be enlarged due to other causes than malignancy. For clarifying this more accurately endobronchial ultrasound-guided needle aspiration can be performed. Radial endobronchial ultrasound can be helpful in determining the depth and the extent of tumor invasion in an airway and hence better suited for endobronchial management (119;120). Coupling ultrasound and needle aspiration with other modalities, such as autofluorescence, narrow band imaging, or other imaging techniques allows for even better differentiation of localized versus spread malignancy (121).

Bronchoscopic eradication may become an initial stage of treatment in selected cases of potentially resectable intraluminal typical carcinoid, but such approach may have a certain risk for subsequent recurrence, and there is a need for randomized, controlled studies on bronchoscopic treatment with long-term follow-up (122). Until then, surgical resection remains the treatment of choice in patients with bronchial carcinoid. Survival after surgical treatment has been shown to be excellent and complications rare (123).

6.2.4 Impact of bronchoscopic treatment on quality of life, lung function and dyspnea

The results from Paper III indicate that the effect of bronchoscopic treatment on quality of life and dyspnea is significant and persistent, even 2 months after the procedure. The patients seem to have less fatigue initially, but this effect was not detectable after 2 months. Given that patients with malignant airway obstruction have a sinister survival prognosis of approximately 3 months after treatment, and that it is difficult to achieve a clinically meaningful improvement in quality of life with the use of other treatment modalities (124;125), one can conclude that even a temporary stabilization of quality of life would be an important outcome of bronchoscopic treatment in these severely ill patients. Results from other studies support our findings (86;126).

When compared to the other lung cancer populations, the patients referred to interventional bronchoscopy treatment tend to have worse quality of life both before the endoscopic treatment. This is understandable as these patients would have a substantial airway obstruction. However, two weeks after the treatment the endoscopic treatment group showed no significant difference in quality of life compared to the advanced stage lung cancer population (stage 3 and 4), meaning that their quality of life was no worse than in other lung cancer patients. This is an important achievement in our opinion. Unfortunately, already 2 months after endoscopic treatment, quality of life in our study population returned to the pretreatment level.

Interventional bronchoscopy gives a significant improvement in lung function. The difference, even being statistically significant, may not seem so impressive at a closer look. One can wonder, how likely it is that a patient would notice a 6–8% improvement in any of the pulmonary test indices. However, this improvement is proven to be not only statistical, but also of a clinical significance. Some of the patients got excellent results after bronchoscopic treatment with improvement in lung function, whilst some cases the lung function got worse. This effect could also be partially explained by a placebo effect. Scientific proof is difficult to obtain since a randomized clinical trial is unacceptable for ethical reasons, as discussed above. One should remember that it can take some time before the lung tissue gets its functionality after re-opening the airflow, and that may also be reflected in lower rate of functional test improvement in some of the patients.

As shown in Paper I, many patients admitted to endoscopic treatment were dependent on use of oxygen; most of these patients could be discharged without oxygen after interventional procedures. Three out of four patients that were on mechanical ventilation at admission could be discharged after the treatment. Although one could not measure their quality of life with a questionnaire, it seems obvious that all these patients that had a significant effect of bronchoscopic treatment.

6.2.5 Management of patients with critical airway obstruction

Critical airway obstruction in our material was characterized by stridor, narrow tracheal lumen < 5 mm on CT scans, stenosis of both main bronchi, or events during the procedure that lead to airway obstruction, such as tumor swelling, or tumor fragments or blood clots obstructing trachea and/or both main bronchi.

The choice of airway device during general anaesthesia normally is made at the anaesthesiologists discretion, but in patients undergoing interventional bronchoscopy, it is necessary to place a large-bore tube above the stenotic lesion to allow instrumentation. The choice of airway device, and the possible change of strategy during the procedure, should be discussed and planned by the bronchoscopist and the anaesthesiologist before the procedure.

The choice of airway will depend on the type and location of the lesion, as well as on the planned procedure. Standard orotracheal tube was used in more than two thirds of the patients in Paper IV. Ventilation with an laryngeal mask is an option to endotracheal intubation in patients with proximal tracheal pathology (127). The laryngeal mask is placed above the vocal cords, which gives good access for subglottic procedures (128). Additionally, the lumen of the laryngeal mask airway is large enough to introduce the bronchoscope without obliterating the ventilating lumen (129). In our case series, laryngeal mask airway was the second most used airway type (10% of the cases), with few problems.

In patients with critical airway obstruction either detected before or occurring during the procedure, the choice of airway was somewhat different than for the other patients. Laryngeal mask airway was used more frequently due to the occurrence of high tracheal lesions requiring high tracheal instrumentation. In one third of the patients with critical airway stenosis or obstruction the airway was changed. In some cases this was due to poor ventilation conditions, but was most often associated with a need for improved operating conditions - changing to a rigid bronchoscope to allow the use of larger forceps or coring, or changing the tracheostomy cannula to a larger tube.

6.3 CONCLUSIONS

Interventional bronchoscopy is a safe tool with low complication rate in the hands of an experienced operator. Interventional endoscopic procedures have almost immediate effect, which is important in patients with malignant airway obstruction, since their life expectancy is short. What can be more important, these methods can improve lung function and quality of life in these critically ill patients. Ventilation problems are the main anesthesiological challenge during interventional bronchoscopy. Multidisciplinary team approach with close collaboration and communication between interventional pulmonologists, anesthesiologists and operation room staff is therefore essential.

6.4 FUTURE PERSPECTIVES

2.2.4 Future Perspectives of Interventional Bronchoscopy

The future of interventional bronchoscopy seems to be promising and recent years have been an exciting time for interventional pulmonologists as these methods continue to expand their boundaries (130). As the lung cancer epidemic continues, and for the foreseeable future patients will continue to present with malignant central airway lesions that require ablative therapy or stenting. Many newer tools within the field of interventional bronchoscopy have already found their place in everyday clinical practice both for treatment and diagnosis (119;131-133), and we are looking forward to see new advances in bronchoscopic techniques in the nearest future.

Interventional bronchoscopy practice should become more evidence based. Most of the evidence supporting the use of interventional techniques has arisen from retrospective reviews and single-institution case series. There is a need for more studies comparing outcome in different groups of patients and with different treatment modalities. Interventional bronchoscopy research is shifting to randomized, controlled multicenter studies, often with sham controls (90;134;135). This type of research can best serve patients and can only lead to improved stature of interventional bronchoscopy within the medical world.

The authors' belief is that advances in technology and further development of bronchoscopic equipment in the nearest future will contribute to better diagnosis and treatment possibilities as well as wider use of these methods in clinical practice.

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