Stereotactic Body Radiotherapy in Non-Small Cell Lung Cancer

Pia Baumann
"Life may not always be the party we hoped for but while we are here we might as well dance"

-Unknown

To my Father and to my Family
"Vinden och vågorna är alltid på den skickligaste sjömannens sida"
- Edward Gibbon
ABSTRACT

Patients with stage I non small cell lung cancer (NSCLC) are potentially curable. Eradicating the primary tumour is a prerequisite for cure with surgery as standard treatment. A large part of NSCLC patients, in parallel to their cancer, also suffer from other smoke related diseases like chronic obstructive pulmonary disease (COPD) and cardio vascular diseases (CVD). In about 15 % of the patients with stage I NSCLC these coexisting diseases confer inoperability. With conventionally fractionated radiotherapy (CFRT) local tumour control is obtained in less than 50% of stage I NSCLC patients. This is related to limitations in permisive dose mainly due to risk of unacceptable toxicity in surrounding normal lung parenchyma. With stereotactic body radiotherapy (SBRT) doses high enough to sterilize the tumour, without excessive toxicity in normal tissue, can be delivered. The aim of this doctoral thesis and the underlying papers has mainly been to collect clinical evidence for a role of SBRT in the treatment of NSCLC.

In the thesis, outcome and toxicity were analyzed in a retrospective and a prospective study on stage I NSCLC in altogether 195 patients treated with SBRT. COPD or CVD was the main reason for inoperability among the patients. The total radiation doses given had a median peripheral biologic effective dose (BED,α/β) of 113 Gy and a central dose of 2110 Gy. Median follow up was 3 years. Local tumour control rate was 88% in the retrospective (ret.) and 92% in the prospective (pro.) study. Only 5% (ret.) and 7% (ret.) of the patients experienced regional failure. During follow up, distant metastases were recorded in 16% (pro.) and 25% (ret.) of the patients. Overall survival at 3 years was 52% (ret.) and 60% (pro.) but lung cancer specific survival was 66% (ret.) and 88% (pro.), a difference that is likely explained by death due to co-morbidity.

To further develop SBRT a better understanding of the risk of toxicity is needed. This is especially important in patients with COPD who already have an impaired lung capacity. On the whole, toxicity after SBRT was mild and in 59% (ret.) and 21% (pro.) of the patients no side-effects were recorded. Objective lung function measured as forced expiratory volume in 1 second (FEV1%) did not decrease more than what is expected in a non-irradiated patient cohort, during the follow-up period. Clinically important toxicity was seen in 10% (ret) and 30% (pro.) of the patients. Dyspnoea and thoracic pain were most common. No significant difference was seen between COPD and CVD patients. Notable is that COPD patients with the poorest lung function tolerated SBRT to the same extent as other patients. In SBRT of lung tumours no established relationship between dose-volume parameters and the incidence of clinical radiation pneumonitis (RP2+) has been shown which is contradictory to the situation with conventionally fractionated radiotherapy (CFRT). Dose-volume-histogram (DVH) and toxicity data from the prospective study was used for normal tissue complication probability (NTCP) modelling. DVH data was corrected to 2 Gy/fraction using the universal survival curve (USC) model as well as the LC model with α/β of 3 Gy and 20 Gy. In SBRT of lung tumours NTCP modelling with USC used for fractionation correction, resulted in a more serial architecture of functional subunits in the lung than what is seen after CFRT.

In conclusion, SBRT for early stage lung cancer provides local control rates similar to what is obtained with surgery. SBRT is also well tolerated with limited side-effects even in patients with markedly decreased pulmonary function. The calculated risk of pneumonitis, using the models in this study, depended relatively more on the volume with the highest doses than what is seen after CFRT. Overall survival is favourable compared to other nonsurgical treatments and lung cancer specific survival is excellent and with these results it is reasonable to conclude that SBRT should be offered to medically inoperable patients with stage I NSCLC.
LIST OF PUBLICATIONS

I. **Pia Baumann**, Jan Nyman, Ingmar Lax, Signe Friesland, Morten Hoyer, Suzanne Rehn Ericsson, Karl-Axel Johansson, Lars Ekberg, Elisabeth Morhed, Merete Paludan, Lena Wittgren, Henrik Blomgren and Rolf Lewensohn
Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries
*Acta Oncologica*, 2006; 45: 787-795

Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer – A first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study

Outcome in a prospective phase II trial of medically inoperable stage I NSCLC patients treated with stereotactic body radiotherapy (SBRT) Accepted for publication in *Journal of Clinical Oncology (JCO)*, Feb 2008

IV. Berit Wennberg, **Pia Baumann**, Giovanna Gagliardi, Pehr Lind and Ingmar Lax
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LIST OF ABBREVIATIONS

BED  biologic effective dose
CCI  Charlson co morbidity index
CFRT  conventionally fractionated radiotherapy
COPD  chronic obstructive pulmonary disease
CR  complete remission
CT  computed tomography
CTC  common toxicity criteria
CTV  clinical target volume
CVD  cardiovascular disease
DVH  dose volume histogram
DLCO  Diffusion capacity carbon monoxide in the alveolar membrane
EUD  equivalent uniform dose
FEV1  forced expiratory volume in 1 second
FEV1%  predicted value of forced expiratory volume in 1 second
18F-FDG  18F-Fluorodeoxyglucose
GCP  good clinical practice
GCD  ground glass opacity
GTV  gross tumour volume
LQ  linear quadratic
LKB  Lyman-Kutcher-Burman
NSCLC  non-small cell lung cancer
NTCP  normal tissue complication probability
MLD  mean lung dose
PB  pencil beam
PD  progressive disease
PE  Pleural effusion
PS  Performance status
PET  positron emission tomography
PR  partial remission
PTV  planning target volume
QoL  Quality of Life
RP2+  radiation pneumonitis grade 2 or more
RS  radiosensitivity
RTOG  radiation therapy oncology group
SBRT  stereotactic body radiotherapy
SBF  stereotactic body frame
SD  stable disease
SHMT  single hit multi target
SRS  stereotactic radio surgery
TNM  tumour, lymph nodes, metastases
TC  tumour control
USC  universal survival curve

biologic effective dose
Charlson co morbidity index
conventionally fractionated radiotherapy
chronic obstructive pulmonary disease
complete remission
computed tomography
common toxicity criteria
clinical target volume
cardiovascular disease
do se volume histogram
Diffusion capacity carbon monoxide in the alveolar membrane
equivalent dose in 2 Gy fractions
equivalent uniform dose
forced expiratory volume in 1 second
predicted value of forced expiratory volume in 1 second
18F-Fluorodeoxyglucose
good clinical practice
ground glass opacity
gross tumour volume
linear quadratic
Lyman-Kutcher-Burman
non-small cell lung cancer
normal tissue complication probability
mean lung dose
pencil beam
progressive disease
Pleural effusion
Performance status
positron emission tomography
partial remission
planning target volume
Quality of Life
radiation pneumonitis grade 2 or more
radiosensitivity
radiation therapy oncology group
stereotactic body radiotherapy
stereotactic body frame
stable disease
single hit multi target
stereotactic radio surgery
tumour, lymph nodes, metastases
tumour control
universal survival curve
1. INTRODUCTION

Stereotactic body radiotherapy (SBRT) has been in use at Karolinska since the beginning of 1990ies and is an exact and efficient way of delivering high ablative radiation doses with high precision to localized targets in the lung and other areas in the body. Like always with new unexplored methods the first category of patients treated with SBRT were in a medical condition where no other treatment option existed. The most common patient had a lesion in the lung and many had primary lung cancer (LC), medically inoperable due to co-existing diseases like chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD). The first treatment results with SBRT resulted in optimism with few side-effects and good local tumour control.

For early stage non-small cell lung cancer (NSCLC) surgery is still the treatment of choice and in retrospect medically inoperable patients who could tolerate a treatment session of 6 weeks were referred to conventionally fractionated radiotherapy (CFRT). Patients with poor performance status received, in general, no active oncologic treatment at that time but at Karolinska were they offered SBRT, which slowly became the standard of care for all medically inoperable early stage I NSCLC at this centre. No randomized study comparing SBRT and CFRT was performed to support this change in standard treatment. Instead the excellent results in tumour control, the minimal toxicity and the convenience for the patient (a treatment period of 1 week with SBRT) seen in the clinical setting contributed to the decision to use SBRT for selected cases. SBRT spread rapidly to other centres in the world where similar experience was reported and the method was accepted for medically inoperable stage I NSCLC.

Several small retrospective studies were published but none reported results from larger prospective series. In a Nordic collaboration between five centres in Sweden, one in Denmark and one in Norway, a prospective phase II study was designed. At the same time collection of retrospective data of SBRT started in order to broaden our knowledge and provide evidence to support the treatment results of our earlier clinical observations. The present thesis is primarily based on the experience from these studies.

To optimize the possibility for a successful treatment with SBRT some important requirements have to be fulfilled. A summary of these together with a background of radiotherapy and lung cancer will be presented in the first sections followed by a summary of the studies including patient and treatment characteristics, methods, results, discussion and a conclusion with a proposal of future directions of SBRT in NSCLC.
1.1. RADIOTHERAPY

Soon after Conrad Roentgen’s discovery of x-rays in 1895, radiation therapy (RT) for tumours was initiated mainly delivering single fractions resulting in good tumour response and tolerable acute side effects. RT was empirically developed during the following years. Unfortunately occurrence of unacceptable late effects with poor wound healing, ulceration, stenosis, contractions in devascularized, denervated and devitalized tissue in treated areas showed up. However, the technique for dose delivery was immature with inability to decrease exposure to for example skin due to low dose energies utilized (KeV) and the target area included large amounts of normal tissue necessary to be included to avoid tumour misses. An alternative way to achieve tumoricidal total doses was to deliver smaller fractions of RT during a period of time and already in 1906, Bergonie and Tribondeau formed the biological basis for fractionization of the radiation dose. It was not until 1930 a general replacement of hypofractionated RT with fractionated radiotherapy with curative intent took place. With conventionally fractionated radiotherapy (CFRT), multiple fractions of 1.5 – 3 Gy (usually 2 Gy) are delivered daily (except for week ends) over a period of 3-7 weeks. This strategy was based on the first radiobiological models where the tumour was assumed to differ in radiosensitivity when compared to healthy tissue resulting in increased risk of damage and decreased repair capacity in tumours compared to normal tissue. With this aspect in mind a therapeutic window was envisaged where the time between every fraction dose will favour the recovery of the normal tissue in the target area.

During many years, the standard radiation dose used in NSCLC was 60 Gy delivered as CFRT during 6-7 weeks. With this dose only 40-70% of the patients with stage I NSCLC received local tumour control and the conclusion from published studies was that the radiation dose was insufficient to control the majority of the tumours.

Improved local control can be achieved with:

a. Increase of the total dose
b. Increase of the dose/fraction
c. Increasing radio sensitivity by combining with chemotherapy or other radio sensitizing agents e.g. targeted drugs.

With older RT techniques, dose escalation was not possible due to unacceptable normal tissue toxicity. Today, with better precision of dose delivery, higher energies (MeV) and improved imaging methods, several dose escalating studies have been performed showing that doses up to 84 Gy can be tolerated. However, no definite dose response relationship was seen and loco regional failure was still observed in 50-78% of the patients. It is proven that doses up to 100 Gy, with certain dose-volume restriction, nowadays can be delivered with CFRT but higher doses do not seem to improve local control which in itself is strongly connected with survival. The reason may be the protracted overall treatment time where a treatment prolongation over 5-6 weeks can result in a loss of 1-2% survival/day, explained by accelerated tumour clonogen repopulation. There is also an increased risk of treatment interruptions.
with a prolonged treatment time which per se is shown to increase the risk of death with 2% for each day of prolongation of the therapy. Hypofractionation with an accelerated scheme (CHART\textsuperscript{14,15}) resulted in increased rates of local control and survival but this regimen was not implemented in most centres since results from contemporary studies, published at the same time, showed substantial evidence that platinum-based chemotherapy combined with conventionally fractionated radiotherapy was superior to radiotherapy alone. As a result, the combined modality approach became standard practice in many parts of the world.

An increased dose per fraction is used in stereotactic body radiotherapy and is based on small target volumes including limited amount of normal tissue in the radiation field. The risk of late toxicity is, however, known to be increased in late reacting tissue with large fraction doses.\textsuperscript{20-24}

With concomitant radio-chemotherapy radiosensitivity is augmented and this strategy is today standard for larger radiation fields, which are necessary for covering the tumour extension (e.g. inclusion of affected lymph node stations) in stage III NSCLC \textsuperscript{25}. Concomitant radio chemotherapy or chemotherapy alone is not recommended in stage I NSCLC. Yet, for patients with T2 disease adjuvant chemotherapy after surgery is becoming standard with a survival benefit of approximately 5% at 5 year. \textsuperscript{26-22}

Randomized controlled trials are the golden standard when introducing a new treatment strategy but so far no one has performed this kind of study for SBRT since the difference in local tumour control compared to CFRT in early treatments series without control groups was immense and the convenience for the patient was too low for achieving good local tumour control and this doses are not comparable to the doses used in SBRT. The Nordic SBRT study group therefore designed a randomized study comparing CFRT with 70 Gy in 2 Gy fractions to SBRT with 66 Gy, delivered to the isocentre, in 3 fractions (SBTACE). The study is still ongoing.

\subsection*{1.2.1. BACKGROUND}

Development of stereotactic body radiotherapy (SBRT) was inspired by stereotactic radiosurgery (SRS) of intracranial lesions. Already in 1951, Lars Leksell, a neurosurgeon at Karolinska University Hospital, described the procedure of how to irradiate a small intracranial located volume with a high single dose. The work was initiated by attempts to reduce damage from diagnostic procedures or surgical procedures. To reduce the entry damage when a biopsy or a smaller operation was performed, Leksell developed an instrument, based on a stereotactic coordinate system, to guide surgical instrument to a specific point. In order to further reduce damage in the normal tissue caused by surgery, this system was adjusted for radiotherapy use. The first “Gamma Knife” was produced and in work 1967. With this technique up to 201 non-coplanar procedures or surgical procedures. To reduce the entry damage when a biopsy or a smaller operation was performed, Leksell developed an instrument, based on a stereotactic coordinate system, to guide surgical instrument to a specific point. In order to further reduce damage in the normal tissue caused by surgery, this system was adjusted for radiotherapy use. The first “Gamma Knife” was produced and in work 1967. With this technique up to 201 non-coplanar
beams are intersecting at the target volume and as a result the dose to the surrounding tissues is minimized. Photons of gamma rays (Gamma Knife) is still the most common way to provide the radiation but also X-rays produced by a linear accelerator (LINAC) and protons (heavy particles) produced by a cyclotron are being used. The aim of SRS is the destruction of all cells in the targeted volume in order to control/stop the growth or reduce the volume of benign or malignant tumours, to provoke tissue changes leading to the occlusion of blood vessels in arterio-venous malformations, or to improve certain functional abnormalities. The treatment proved to be safe, convenient for the patients and very effective with a local control of 90% when tumours were treated. Not uncontroversial and quite opposite to conventional radiotherapy, a margin for microscopic tumour spread (GTV-CTV) was not used even for malignant tumours in SRS.

At the beginning of the 1990s there was considerable experience at Karolinska from the treatment of CNS metastases from different solid tumours using the Gamma Knife. At that time a physicist dr Ingmar Lax and two physicians dr Henrik Blomgren and dr Ingemar Näslund, also at Karolinska University Hospital, developed a methodology for stereotactic body radiotherapy (SBRT) based on two hypotheses. First, intracranial metastasis can be treated successfully by SRS without margin for microscopic spread; similarly, metastases in the body from the same primary tumours should also be possible to treat with essentially no margin for microscopic spread. Second, hypofractionation with high total doses, without exceeding toxicity limits in normal tissue, to moderately large metastases in the body would be possible to use, at least in large host organs such as lung and liver.

In 1991 additional adjustment of SRS were made to make it fit for tumours in the body. The method of SBRT developed into what is described in the treatment section. The first patients were treated for metastases in the liver and the lungs. The initial results were encouraging with sometimes remarkable tumour responses and low toxicity, but the optimal fractionation pattern was largely unknown. During the following years, SBRT slowly but gradually developed by increasing clinical experience and from the mid 1990s a hypofractionation pattern with usually three fractions was established. The clinical experience from the Karolinska University Hospital was also confirmed by data from Uematsu et al in Japan, who independently introduced SBRT three years after Karolinska. During the second half of the 1990s training courses in SBRT were given at Karolinska. By this way a relatively uniform methodology and fractionation pattern was disseminated to several centres in Europe and USA. This facilitated the comparison of results from different centres. The high local control rates, after SBRT of metastases promoted the hypothesis that even primary tumours in the lungs and liver could be treated with no or very small margins for microscopic spread. SBRT for inoperable stage I NSCLC was introduced in 1995.

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1.2.2. TREATMENT PROCEDURE

The procedure to deliver SBRT originates from SRS as described in the background section. There is however, a large difference in the treatment of targets in the brain and targets in the body related to the movements of the body produced by for example breathing and circulation. The first SBRT technique involved a stereotactic body frame where the tumour was visualized and localized in a 3D-coordinate system using a CT-scan and the tumour movement was reduced by compression of the abdomen. Today additional ways are developed which allow accurate dose delivery when using a very high dose per fraction in SBRT. The different procedures have some denominators common, which are small margins GTV/CTV and CTV/PTV, consideration of breathing motions, geometrical verification of the target position and hypofractionation. Methodological and technical differences exist within:

- Imaging for treatment planning
  - Slow CT scanning to produce an internal target volume (ITV)
  - 4D-CT to produce an ITV and mid ventilation position (MIP)

- Consideration of breathing motions
  - Abdominal compression to reduce tumour motion
  - Voluntary breath hold
  - Active breathing control
  - Gating in the dose delivery
  - Tracking of the target

- Set-up and geometrical verification
  - Stereotactic body frame and 3D-CT
  - CT (MV or kv) at the accelerator (Cone Beam CT)
  - Projection imaging (MV or kv) of markers in the target

Slow CT scanning is an uncomplicated method to achieve a relatively good estimate of the internal target volume (ITV). When using imaging with 4D-CT, ITV is derived from the union of the GTV delineations of all breathing phases or alternatively from contouring a maximum intensity projection (MIP) CT- dataset, which takes into account the whole tumour movement. Using the mid-ventilation phase, where the tumour is located most of the time during the respiration cycle, is an alternative way of defining the target. With these techniques the mobility of the tumour can be considered both for imaging and treatment. Abdominal compression is commonly used due to its simplicity and efficiency to reduce breathing motions. In a recent study of 1332 patients treated with abdominal compression the cranial caudal motion was reduced to be within 10 mm in 73% of the cases, 12 mm in 87% of the cases and 15 mm in 95% of the cases. Voluntary breath hold techniques and active breathing control is used at some centres and the patients seem to be able to cooperate and tolerate the method. The treatment time is, however, prolonged and could lead to inferior tumour control. Data on gating has not been sufficient regarding target reduction and tumour control and is rarely recommended. Tracking of the tumour can be done by means of the multileaf collimator (MLC) or by moving the treatment couch or the accelerator synchronously with the target motion. A presumption for this is that the breathing motion has been modelled.
The set-up and geometrical verification procedure was initially performed as described below. Later on, projection or topographic imaging with MV or kV beams at the accelerator was introduced. The projection imaging is commonly based on interventional marker placement into the target, applied before the first CT. The daily imaging procedure is used for the correct set-up.

The methodology for SBRT originally developed at the Karolinska University Hospital was used by all centres in the Nordic SBRT study group, participating in the SBRT studies performed (Study I, II and III). In this way the treatment has been conformal and the evaluation of the results consistent.

This SBRT method is built upon five cornerstones:

1. Stereotactic methodology for imaging and treatment set-up
2. CT verification of the tumour position in the stereotactic reference system
3. Reduction of tumour motions
4. Heterogeneous dose distribution in the planning target volume
5. Hypofractionation

Dos 67\% PT V CT V
15 Gy x 3
12 Gy x 4
The materials in the frame are wood and plastic in order to minimize artefacts in CT images. The patient is supported by means of a vacuum pillow. A devise for abdominal compression is attached to the frame which can be used to minimize respiratory movements. The length of the pillow extends from the head to the upper parts of the thighs. Copper indicators on the inside of the frame are visible on the CT images which permit x, y and z coordinate determinations for the localization of the target. For correct isocenter positioning in the treatment room, scales on the outside of the frame are used.

Preparation before treatment planning

The patient is placed supine on the vacuum pillow located in the SBF. The air of the pillow is then pumped out to form a rigid cast of the patient’s body. Thereafter a fluoroscopy of the chest is performed. The movements of the tumour and the diaphragm are observed during normal breathing. If the tumour movement is more than ±5 mm, pressure is applied on the upper abdomen. If the tumour is not visible with fluoroscopy the diaphragm movement is measured in a similar way as the tumour. The pressure is adjusted, in order to minimize the diaphragmatic movements, as well as, the cranio-caudal movements of the tumour, to be within ±5 mm. A CT examination of the chest and the upper part of the abdomen with the patient positioned in the SBF is then performed. Of importance for this method is that the positioning of the patient into the stereotactic frame is highly standardized, to be the same at the CT and the treatment unit.

Target definition and delineation

The definition of the target is done on the CT images where the extension of the tumour is identified. Gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV) are delineated on each axial CT image using pulmonary windowing (1000 Hu to about 500 Hu). However, soft tissue windows are additionally used to avoid inclusion of adjacent vessels or chest wall structures within the GTV. The correctness of the GTV delineation is verified in axial, sagital and
The clinical target volume (CTV) was in the retrospective material identical to GTV (study I). In the prospective study, CTV comprised the GTV with a margin of 1-2 mm for microscopic disease (study II and III). Based on previous experience a margin of 5 mm in the transversal plane and 10 mm in the longitudinal plane is added around the CTV to define the planning target volume (PTV). For tumours less than 3 cm in diameter and not adherent to the pleura the margin in the transverse plan is 10 mm. The CT is done with a speed of 1-2 seconds per revolution. Thus the scanning time of the tumour is sufficient to cover a breathing cycle. In this way the CT imaging gives a relatively good estimate of the breathing induced target motion. It could be argued that the term internal target volume (ITV) should be used instead of CTV when defining the target in this way. However, the scanning speed of the CT is too high to give an exact measure and an exact ITV is not possible to create.

Treatment planning

All patients included in the present studies were planned with pencil beam algorithms with heterogeneity correction using 6 MV photons, in the Helax-TMS or Eclipse systems. A 3D static conformal multifield technique was used. The beams were shaped with multi leaf collimators to conform to the projection of the PTV in the different directions of the beams. Usually five to nine coplanar and/or non-coplanar beams were used and they were spread in a large angular interval in order to decrease the dose to surrounding lung tissue. Similar to the intracranial SRS, a deliberate inhomogeneous dose distribution with the highest dose in the central portion of the PTV was aimed at. This was achieved by using fields smaller in size than the extent of the PTV. A very high dose is thus obtained within the target with a rapid dose fall off just outside in the normal surrounding tissue. An advantage of the extremely high doses in the central part of the tumour is that this may overcome the increased radioresistance in the more hypoxic compartments. The dose was prescribed and specified to the 67% isodose at the periphery of the PTV. Figure 1 illustrates the dose distribution, here normalized to the periphery of the PTV.

![Figure 1. Schematic illustration of the heterogeneous dose distribution with 100% of the prescribed dose at the periphery of the PTV with an increase in dose to about 150% in the centre of the target.](image1)

Coronal views. The clinical target volume (CTV) was in the retrospective material identical to GTV (study I). In the prospective study, CTV comprised the GTV with a margin of 1-2 mm for microscopic disease (study II and III). Based on previous experience a margin of 5 mm in the transversal plane and 10 mm in the longitudinal plane is added around the CTV to define the planning target volume (PTV). For tumours less than 3 cm in diameter and not adherent to the pleura the margin in the transverse plan is 10 mm. The CT is done with a speed of 1-2 seconds per revolution. Thus the scanning time of the tumour is sufficient to cover a breathing cycle. In this way the CT imaging gives a relatively good estimate of the breathing induced target motion. It could be argued that the term internal target volume (ITV) should be used instead of CTV when defining the target in this way. However, the scanning speed of the CT is too high to give an exact measure and an exact ITV is not possible to create.

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![Figure 1. Schematic illustration of the heterogeneous dose distribution with 100% of the prescribed dose at the periphery of the PTV with an increase in dose to about 150% in the centre of the target.](image2)
Figure 2. Schematic illustration of the difference in dose fall-off between SBRT to the left and CFRT to the right. With an inhomogeneous dose distribution in the target a rapid dose fall-off outside the target can be created. In CFRT a homogenous dose distribution inside a larger PTV results in a slow dose fall-off outside the target.

Figure 3. A dose plan for a small peripheral NSCLC showing the dose distribution both inside and outside the PTV. The blue line represents the prescription dose 100%, the green line is 75%, the yellow line is 50% and the white line is 25% of prescribed dose. A hot spot (150% of the prescribed dose) within the PTV is represented by the small red oval.

Treatment delivery and geometrical verification

The first treatment is given within two weeks after the dose planning CT. Immediately before the first treatment a new CT examination is performed in order to check the reproducibility of the tumour in the stereotactic coordinate system. The limits are set to 5 mm in the transversal plane, and 10 mm in the longitudinal direction. If the deviation is larger, a second CT is done. If the results of the second CT are within the limits, the treatment is delivered. If the results of the second CT are outside the specified limits, a new dose plan with larger margins is done. If the first verification CT


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is outside these limits, and the second verification CT is within the specified limits, a new verification CT is done before all the remaining treatments, as well.

The patients were treated with 10 - 20 Gy x 2 - 4 in the retrospective material and with 15 Gy x 3 in the prospective study. The treatments were given 2-3 days apart in general. The dose was specified to the 67% isodose at the periphery of the PTV. A treatment session lasted about 30–40 minutes depending on the complexity of the treatment plan.

1.2.3. RADIOBIOLOGY

Cell and tissue radiosensitivity (RS) are correlated with the frequency of mitoses and poorly-differentiated and fast proliferating tissues are more radiosensitive than well-differentiated and slow-proliferating tissues. This, together with results of in-vitro models where clonogenic capacity post irradiation was evaluated, created the basis for much of today radiobiological rational. Various modelling parameters have been used to describe the RS of tumour or normal tissue of which the α/ß parameter is most frequently utilized. The shape of the linear quadratic (LQ) survival curve is determined by the ratio α/ß, which thus describes the RS of the specific tissue. The difference in RS among tumour cell lines is illustrated by their different survival curves where d is the radiation dose.

With the LQ model the cell survival curve can be fitted by:

\[ SF = e^{-d\alpha} \]

where d is the radiation dose.

The mechanistic interpretation of this model is that the linear component (αd) is due to single track events in the DNA, while the quadratic component (ßd^2) arises from two-track events.

The α/ß ratio for a given tissue is a rough median value. In fact there is a large spread which becomes evident when tumour cell lines of different histological entity are tested for their RS. In healthy tissue, e.g. fibroblast cell lines, the variation is less. In radiobiology, additional 4 "Rs" besides radiosensitivity explain the survival curve:

- Repair of sublethal damage
- Repopulation with regeneration of normal tissue cells (and tumour cells)
- Redistribution of tumour cells that initially are in a resistant phase will precede though the cell cycle into a more radiosensitive phase.
- Reoxygenation of the hypoxic/necrotic areas.

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1.2.3.1. Fractionation

The use of fractionation in radiotherapy was empirically established. Initially, single dose treatments were used but it soon turned out that small daily doses delivered over a longer period of time resulted in equally good tumour control with less severe side effects. This is explained by the less effective repair capacity in tumour cells compared to normal tissue and this difference is very important in the support of the fractionated regimen.

A major step in the understanding of fractionation was provided by the studies on mice [17] which showed a systematic difference between early responding and late responding normal tissue. Late responding tissues showed to be more sensitive to changes in fraction size than early responding tissues. Tumours usually behave similar to early responding tissues. Later on it was also shown that the isoeffect relationship for normal tissues are consistent with the linear quadratic model and that the $\alpha/\beta$ ratio describe the steepness. Nowadays the linear quadratic model (LQ) [18] approach has become the standard method of calculation in radiotherapy departments.

The biologically effective dose (BED) is used to compare the effects between different dose-fractionation schemes. BED is defined as the total dose delivered in an infinite number of infinitiesimally small dose fractions that has the same biologic effect as the dose-fractionation scheme in question. Complete repair of sublethal damage between fractions is assumed.

$$\text{BED} = \text{D} \cdot (1 + (\text{d} / \text{a} / \text{b}))$$

D is the total dose and d is the dose per fraction.

Two adjacent tissues with different $\alpha/\beta$ ratios (tumour and surrounding normal tissue) and both exposed to the same fractionation regimen, will be associated to two different BEDs. In general, a higher therapeutic index (tumour control (TC) ↑ and normal tissue complication probability (NCTP) ↓) is secured by a tumour BED as high as possible and late-normal tissue BED as low as possible.

1.2.3.2. Hypofractionation

Several questions/reflections arise around the paradigm shift introduced by SBRT. The rational of using conventional fractionation regimens with CFRT is to achieve tumour control and at the same time to limit normal tissue complication. But if the radiation dose could be limited to the tumour, would the rational for conventional fractionated scheme hold? It prolongs the overall treatment time, thus increasing the risk of repopulation of the tumour cells. Furthermore it is inconvenient for the patient and it is expensive. Improved technique of RT delivery with the support of advanced imaging methods will be further developed for use in localized tumours. But how much could the margins around the tumour be minimised without increasing the risk of repopulation of the tumour cells and normal tissue complication? Furthermore it is inconvenient for the patient and it is expensive. Improved technique of RT delivery with the support of advanced imaging methods will be further developed for use in localized tumours.
of missing the microscopic tumour extension? Is the dose spilling outside the tumour responsible for the low incidence of local relapses?

The hypofractionated regimen results in high biologic effective doses (calculated with the LQ model) sufficient enough for tumour sterilizing\(^\text{47-54}\). Yet, the expected efficacy in tumour kill is theoretically jeopardised by the risk of normal tissue toxicity. However, most studies up to now shows that SBRT of peripheral lung tumours results in limited radiation induced complications in normal tissue\(^\text{47,49,52-60}\).

1.2.3.3. Survival curves of the high dose region

The data sets used for fit of the LQ model refer to dose ranges below the biologically ablative doses commonly used in SBRT. The LQ model\(^\text{46}\) predicts a continuously bending curve in the high-dose range, however, experimentally measured data have decidedly shown a linear relationship between the dose and log of the proportion of surviving clonogens\(^\text{41}\). The LQ model works well in the low-dose area but might overestimate the radiation effect of the clonogens in the high doses range. According to the LQ model the survival \(S\) after \(n_1\) fractions with a dose of \(d_1\) per fraction is given by:

\[
S_{LQ} = \exp\left(-\left(d_1 + d_1^2\right)\right)\]

The Single Hit Multi Target (SHMT)\(^\text{61}\) model seem to better fit the empirical data in the high dose region. This model provides an alternative description of the survival curve. It assumes that there are \(\Pi\) targets that need to be hit to disrupt the cell clonogenicity. According to the SHMT model the survival \(S\) after \(n_1\) fractions with a dose of \(d_1\) per fraction is given by:

\[
S_{\text{SHMT}} = \left(1 - \left(1 - \exp\left(-d_2/D_0\right)\right)^{n_2}\right)\]

\(D_0\) describes the slope and \(\Pi\) the extrapolation number of the linear part in a plot of the logarithm of survival versus dose.

of missing the microscopic tumour extension? Is the dose spilling outside the tumour responsible for the low incidence of local relapses?

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A Universal Survival curve (USC), composed of the LQ model for the low doses and the SHMT model at high doses, has been elaborated by Park and colleagues.\(^6\)

![Diagram of Universal Survival Curve (USC)](image)

**Figure 4.** Universal survival curve (USC) is composed of the LQ model in the low dose range and transforms in the high dose range to be identical with the linear portion of the multitarget model at the transition dose \(D_T\). Adapted from Park et al.\(^6\) (with permission).

The USC is built by setting the survival to be the same for the two models:

\[ S_{SHMT} = S_{LQ} \]

The total dose given in \(d_1\) Gy per fraction with the LQ model \(D_{LQ} = n_1d_1\) is given by:

\[ D_{LQ} = -n_2 \ln (\frac{1}{1 - \exp (-d_2/D_0)}) \]

The dose at which the LQ model transits to the SHMT model is called the transition dose \(D_T\).

\[ D_T = 2D_0 \ln (\frac{\alpha}{1 - \alpha D_0}) \]

Where \(\alpha\) is obtained by:

\[ \alpha = \frac{1}{D_0} + 2 \ln (\frac{1}{\alpha D_0} - \frac{\alpha D_0}{\alpha D_0 + 2 \ln (\frac{1}{\alpha D_0})}) \]

Thus, the USC is given by:

\[ \ln S = \begin{cases} (\alpha \cdot d + \beta \cdot d^2) & \text{if } d \leq D_T \\ (1/D_0) \cdot d + \ln (\frac{1}{D_0}) & \text{if } d > D_T \end{cases} \]
Normal tissue can be pictured as composed of microscopic functional subunits (FSUs), each with its own dose-response characteristics. There are two types of FSUs: parallel functioning tissue, with a distinct demarcation between the FSUs (alveoli/capillary in the peripheral lung) independently performing their function (gas exchange); and serially functioning tissue, with no separation between the FSUs which act together to function (mucosa of the oesophagus).

Parallel functioning tissues are typically very large (peripheral lung, peripheral liver, peripheral kidney) and have an inherent reserve capacity where toxicity is mainly related to irradiated volume. In parallel tissue a partial loss of function is therefore tolerable where the parallel tissue is described as having a strong volume effect. Linear and hollow structures like the spinal cord, the oesophagus and the bowels are built up with serially functioning tissues and here the risk of toxicity is probably more dependent on the delivered dose. The serially organized tissue has a limited volume effect.

Most organs are actually a mixture of parallel and serially functioning tissue. The lung is certainly a mixture where the main bronchus works as a serially functioning tissue (late toxicity): a lethal injury will cause disruption of function in all distal parts that connects to that bronchus while a lethal injury in a segmental bronchus will only cause damage to a smaller part of the lung distally located. With this follows, that not only the dose but also the position of the damage in serially functioning tissue will affect the extent of the injury. In the periphery of the lung, where the alveoli and bronchioles are situated, the architecture of the tissue is more parallel functioning (acute toxicity) with FSU working separately.

Several data on radiation induced lung complications have been collected and analysed. The material in the studies stem from a heterogeneous group of patients with a large number of diagnoses: breast cancer, lung cancer, Hodgkin’s disease etc. The dose distributions and the portions of irradiated lung are therefore quite different between the patients. Most analyses refer to pneumonitis grade 2 or higher (RP2+) but some studies have focused on sub clinical radiological changes after irradiation. In general a consensus both on dosimetric predictors and parameterization of the dose-volume response curve has been obtained. Mean lung dose (MLD) was found to be associated to the incidence of pneumonitis and so was V20 (the irradiated lung volume receiving at least 20 Gy). In a phase I dose escalation study by Yorke et al, MLD as well as V20 correlated also significantly.
to the incidence of radiation pneumonitis but the best correlation was with $V_{20}$, $V_{30}$ and $V_{10}$ \( \text{Gy} \). The association of MLD to the incidence of radiation-induced lung complications indicates a strong volume effect in the lung. Another result of Yorke’s analysis was that the lower part of the lung was found to be more sensitive to irradiation, as suggested by the animal studies of Travis et al \( \text{70} \) and the analysis of patient material by Bradley et al \( \text{75} \). The reasons for the regional differences in radio-sensitivity are not clearly explained: a possible explanation could be that the gas exchange is more efficient in the lower part of the lung.

The Normal Tissue Complication Probabilities (NTCP) studies on lung toxicity are numerous, and the NTCP parameters describing the dose-volume response curves are also several. A comprehensive review of normal NTCP modelling using different parameters for prediction of radiation pneumonitis was presented by Seppenwoolde \( \text{80} \). The dose-volume response curve, according to the Lyman-Kutcher-Burman (LKB) model \( \text{81,82} \), seems to be described by a $D_{50}$ of ca 30 Gy; a steepness $m$ of 0.37, and a strong volume effect, as indicated by the value of the parameter $n = 0.99$. No significant difference in parameter values was obtained when using other NTCP models. All the studies above refer to conventional dose distributions and conventional fractionation regimens. The LQ model, generally assuming an $\alpha/\beta$ ratio of about 3 Gy, was used for fractionation correction in the referred studies.

In SBRT no well defined dosimetric predictors or NTCP parameters for lung complications are determined yet. A retrospective analysis has, however, recently been presented by the Torino group. Sixty patients (63 tumours) were treated with SBRT doses of 15 Gy x 3 or a single dose of 26 Gy. Grade 1 and grade 2 lung toxicity (RTDG scale) was observed in 86% and 15% of the cases respectively. All dose distributions were recalculated into 2 Gy fractions with the LQ model. MLD correlated to the observed incidence of clinical pneumonitis (RP2+) with a $D_{50} = 19.8$ Gy. This analysis suggests that the volume effect in the lung is important also in SBRT. The dose-response relationship between NTCP and MLD provided a $D_{50}$ of 22.4 Gy which implies an underestimation of the risk of pneumonitis \( \text{82} \).

### 1.2.4. CLINICAL TOXICITY

Toxicity after radiotherapy (RT) is dependent on factors as the total and the fraction dose, the target volume and the individual radiosensitivity and is characterized by an acute and a late phase. Acute effects appears normally in days to weeks after RT and above all in tissues with rapidly proliferating cells such as skin, oesophageal mucosa etc. In the lung acute effects develops later; weeks to months after RT. In some patients the acute effects persists and continues as late effects. Late effect develops in months to year after RT and represents damage to slowly proliferating tissues resulting in fibrosis, vascular damage and necrosis \( \text{83} \). Individual radiosensitivity is known to influence toxicity but studies investigating the factor behind has so far not been conclusive \( \text{46} \).

In CFRT the main dose limiting toxicity is radiation pneumonitis which is an acute reaction with fever, cough, dyspnoe and thoracic pain occurring within weeks to months. It is regarded as an inflammation in the end bronchioles and alveolus to the incidence of radiation pneumonitis but the best correlation was with $V_{20}$, $V_{30}$ and $V_{10}$ \( \text{Gy} \). The association of MLD to the incidence of radiation-induced lung complications indicates a strong volume effect in the lung. Another result of Yorke’s analysis was that the lower part of the lung was found to be more sensitive to irradiation, as suggested by the animal studies of Travis et al \( \text{70} \) and the analysis of patient material by Bradley et al \( \text{75} \). The reasons for the regional differences in radio-sensitivity are not clearly explained: a possible explanation could be that the gas exchange is more efficient in the lower part of the lung.

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In table 1, expected toxicity after SBRT is presented. Dermatitis is an acute skin reaction within 6 weeks after SBRT. It occurs mainly as a mild faint erythema or a dry desquamation. Radiological pneumonitis without clinical symptoms is common and makes the debut about 3-4 months after SBRT. In some radiological studies almost 100% of the patients were diagnosed with non clinical pneumonitis \(^{0.47}\). Most studies report a low incidence of clinical pneumonitis \(^{0.36, 0.38}\) but one study by Yamashita et al differs from the other by reporting the surprisingly high incidence of grade 3-5 radiation pneumonitis of 12% \(^{0.35}\). Esophagitis is rare and the majority of tumours treated with SBRT are peripheral making the dose in this area limited. In some patients emesis and nausea are reported but no reliable physiological explanation exists. Fatigue, which is reported to occur relatively frequent, has no comprehensive explanation as well. Cough is regularly reported and mainly as a mild acute reaction. Many of the patients that had cough before treatment experience the cough to disappear after SBRT. Severe persistent and disabling dry cough can occur after SBRT of tumours centrally located in the lung. Pneumonia has been reported to occur both acute and late after SBRT. In one study by Timmerman et al \(^{0.29}\) four deaths, related to SBRT, due to pneumonia in patients with centrally located tumours was reported. Dyspnoea is a major problem for many of the patients already before start of SBRT and is very difficult to evaluate after the treatment. All individuals have an annually decrease in pulmonary function in older age. Patients with COPD have an accelerated decrease and are at higher risk of having a reduced respiratory function even without SBRT. Nevertheless, dyspnoea is commonly reported after SBRT and is naturally reducing the patients’ quality of life.

### Table 1. Late and acute toxicity after SBRT

<table>
<thead>
<tr>
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<th>Acute</th>
<th>Late</th>
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<tbody>
<tr>
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<tr>
<td>Pneumonitis</td>
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<td></td>
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<tr>
<td>Esophagitis</td>
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<tr>
<td>Emesis/nausea</td>
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<td>Cough</td>
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<td>Fatigue</td>
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<tr>
<td>Hernias</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Rib fracture</td>
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substantially. Atelectasis occurs frequently, mainly late, but is seldom reported as it primarily is situated in the periphery of the lung at a segmental level leaving the patient without symptoms. Clinical important atelectasis develops usually when the main or lobar bronchus has been included in the high dose area. Pleural effusion (PE) can be seen both as an acute and a late reaction after SBRT and is primarily non-malignant. Yet, PE may be a sign of recurrence why a cytological examination of the pleura is recommended. Patients with tumours invading the visceral pleura (T2), where the maximum dose will be concentrated in this area could perhaps be more sensitive of developing pleural effusion. Rigorous pain in the thoracic wall after SBRT is not common but when it develops it is severely disabling. Ordinary analgesic drugs have usually only a limited effect. Alleviation of the pain with opioids may give better relief but needs often to be combined with drugs for neuropathic pain to block the impulses from the peripheral nerves located on the surface of the thoracic wall. In an early state blockage of these nerves with local anaesthetics (peripheral nerve blocks) could be tested. Fibrosis is a late reaction in the lung and is developed in the high dose area in the majority of the patients. The appearance of the fibrosis changes with time after SBRT and can continue for several years. Rib fracture is a late side effect occurring in most of the cases more than 2 years after SBRT. It is mainly subclinical and diagnosed on CT.

Milano et al published recently a review on SBRT studies and concluded that mild fatigue, malaise, cough, dermatitis, acute grade 1 radiographic pneumonitis were common. Late toxicity was uncommon and seen in only 0-7% with grade ≥2 pneumonitis, cough, pulmonary bleeding/haemoptysis, bronchial fistula, pneumonia, pulmonary function decline, airway narrowing, stricture or obstruction, pleural necrosis, chest wall pain, rib fracture, brachial plexopathy, oesophageal ulcer 81.

**Radiological (CT) evaluation of lung toxicity**

The radiation reaction in the lung after CFRT seems to follow a specific temporal sequence with a short period with no change, patchy consolidation within the irradiation fields (radiation pneumonitis), discrete consolidation conforming the irradiated fields followed by solid consolidation (fibrosis) 82. Ground glass opacities limited to an area immediately surrounding the tumour indicates radiation fibrosis. This could continue as consolidation, volume loss and traction bronchiectasis. Consolidation and traction bronchiectasis in 2 cm immediately surrounding the original tumour is classified as mass like. Linear opacity of only 10 mm or less in thickness is classified as scar like 83. This way of classify radiological changes in the lung after CFRT could be modified and also valid as a tool when evaluating post irradiated lung changes after SBRT (table 2).

Milano et al published recently a review on SBRT studies and concluded that mild fatigue, malaise, cough, dermatitis, acute grade 1 radiographic pneumonitis were common. Late toxicity was uncommon and seen in only 0-7% with grade ≥2 pneumonitis, cough, pulmonary bleeding/hemoptysis, bronchial fistula, pneumonia, pulmonary function decline, airway narrowing, stricture or obstruction, pleural necrosis, chest wall pain, rib fracture, brachial plexopathy, oesophageal ulcer 81.

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A classification of pneumonitis and fibrosis both in time and pattern is valuable when trying to correlate clinical symptoms after SBRT to radiological changes and to predict the development or regress of different radiotherapy induced changes in the lung. A re-examination of all CT scans from the prospective study is ongoing and not presented in this thesis work.
1.2.5. RESPONSE EVALUATION

Generally, the analysis of tumour response after SBRT is complicated by problems with interpreting CT scans due to the emergence of radiation induced fibrosis, atelectases etc. A complementary 18F-FDG PET-CT for estimation of the metabolic response in SBRT treated lesions could be of value. Yet, no study has been conclusive in how to evaluated the response on a PET-CT, since both inflammatory processes (pneumonitis, fibrosis) as well as residual or progressing tumour accumulates 18F-FDG. If a tumour relapse is suspected and none of the radiological examinations have been decisive, transthoracic biopsy is recommended.

The tumour status was evaluated with CT and the response was considered as complete remission (CR) if no visible tumour was noted, as partial remission (PR) if the cross sectional tumour area was reduced with at least 50% and stable disease (SD) if there was less than 50% decrease or less than 25% increase. Local failure was defined as > 25% in increase of cross sectional tumour area.

1.3. NON-SMALL CELL LUNG CANCER

The national board of health and welfare published statistics for 2007 showed that 50'000 new cancers were diagnosed in Sweden this year. Even though lung cancer was ranked as number four in women (incidence: breast cancer 29%, colon cancer 8.4%, skin cancer 7.4%, lung cancer 6.5%) and five in men (incidence: prostate cancer 34%, skin cancer 9%, colon cancer 7.1%, urinary organs 6.6%, lung cancer 6.3%) it was the leading cause of cancer death in both sexes. Lung cancer is a significant public health problem and has continuously increased in incidence in women with 3.1%/year for the last 20-years period and 3.6% for the last decade. In men, on the other hand, it is decreasing annually with 0.8% during the last 20-years period but lung cancer is still more common in men than in women (38 compared to 31 cases / 100 000). This is probably due to the change in smoking habits since about 90% of all lung cancer is caused by smoking. Women with lung cancer have a better overall survival than men even if they generally have a more advanced cancer at the time of diagnosis. The life expectancy at birth in Sweden for 2007 was 78.9 years for men and 83.0 years for women. Lung cancer is a disease of old age and is primarily diagnosed from 60-79 years of age. This means that with a life expectancy of about 80 years many patients could still have several years left to live with curative treatment strategies.

Unfortunately, lung cancer patients will, with the therapeutic arsenal we have today, only have a chance for cure if they have a localised disease with no disease spread outside the lung. Surgery is the standard treatment with local control rates of 80-100% and 5-year overall survival rates of 50-70% [8,10]. Local tumour control is strongly connected to survival [8]. Even if the tumour is locally controlled the patients will in about 20% develop progressive disease that may be caused by the presence of undetected occult metastatic disease [10]. This is a major problem that hopefully could be solved with better diagnostic procedures (PET-CT) or by adding of systemic treatment. Yet, no gain in survival with adjuvant chemotherapy for small stage I
tumours (T1) have been seen in former studies 20,22,103. The 5-years survival in all stages of lung cancer is only 5-15% 104.

Lung cancer is primarily divided into two groups; small cell lung cancer (SCLC) (15% of the incidence) and non-small cell lung cancer (NSCLC) (85% of the incidence). Only NSCLC will be discussed in the studies and in detail in the present thesis.

From the Swedish lung cancer registry (2002-2006, 98% coverage) the rates of localised lung cancer (stage I) was about 20% and these patients were considered for curative standard surgery. Seventy four percent of the stage I patients were operable, 16% were considered as medically inoperable and was offered radiotherapy (CBRT or SBRT). 18% received chemotherapy (adjuvant or first line) and the rest of the patients, 7%, had a poor performance status not rendering them any active oncologic treatment 105. Performance status is very important for the outcome and is of course affected by the patients other diseases 106,107. In many smokers chronic pulmonary disease (COPD) and cardiovascular diseases (CVD) develops over time and the severity of these diseases is the main reason preventing operability in stage I NSCLC. The extent of the disease is affected by pack-year but this is not entirely true since some patients can smoke heavily without developing COPD, CVD or lung cancer while others will get it all with minimal or no tobacco consumption 108. Several studies of individual sensitivity have been performed with inconclusive results 109,110.

With the accessibility of improved imaging methods there is hope to improve the diagnosis of NSCLC at early localized stages, possible to cure, instead of disseminated lung cancer in patients with clinical symptoms. To discover the lung cancer at an early stage screening programs for smokers with regular examinations with CT has been proposed. Publications from these studies shows no consensus since the risk that the radiation dose delivered at each imaging occasion itself can promote the development of cancer, must be weighed against the finding of a few small lung cancers 110,111.

1.3.1. CLASSIFICATION AND STAGING

Non-small cell lung cancer (NSCLC) is mainly sub classified in to;

a. adenocarcinoma
b. squamous cell carcinoma
c. bronchoalveolar cells carcinoma
d. large cell carcinoma
e. unspecified NSCLC

During the last decade the frequency of adenocarcinoma has increased and squamous cell carcinoma decreased in Sweden 114. Moreover, adenocarcinoma is more common among women and in non-smokers.
The current system for staging of lung cancer, the TNM system adapted by the American Joint Committee for cancer staging 1997, describes the anatomical spread of cancer by considering the tumour size and invasion, extent of lymphatic spread and presence of metastatic disease. An accurate staging of NSCLC before treatment has important impacts on survival.

The tumours treated with SBRT in the present studies are all stage I NSCLC, which means that they can be either T1 or T2 tumours with no lymph node involvement and no distant metastases. T1 tumours are 3 cm or less in diameter and completely surrounded by lung parenchyma. T2 tumours are greater than 3 cm or exhibit invasion to the visceral but not the parietal pleura. The tumours are not allowed to be located closer than 2 cm from the carina. Atelectasis may extend to the hilus but are not allowed to involve an entire lung (fig. 5).

**Figure 5. Schematic picture of T classification.** The tumours put in brackets represent T1 and T2.
In 2008 a new staging system was proposed after analyzing 68,463 patients with non-small cell lung cancer. Regarding tumour size, survival analysis was done in the population of 7335 patients with pathological T1 and T2N0M0 completely resected tumours. After statistical calculations the optimal cutpoint in stage T1 was set to 2 cm. For T2 tumours two cutpoints was found at 5 and at 7 cm respectively. These cutpoints together with the classic 3 cm cutpoint that separates T1 from T2 tumours, generated five groups of tumours of different size and significantly different survival (table 3).

<table>
<thead>
<tr>
<th>T-stage</th>
<th>Proposed Seventh edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 &gt; 2 ≤ 3 cm</td>
<td>T1a</td>
</tr>
<tr>
<td>T1 &gt;2 ≤ 3 cm</td>
<td>T1b</td>
</tr>
<tr>
<td>T2 &gt;3 ≤ 5 cm</td>
<td>T2a</td>
</tr>
<tr>
<td>T2 &gt;5 ≤ 7 cm</td>
<td>T2b</td>
</tr>
<tr>
<td>T2 &gt;7 cm</td>
<td>T3</td>
</tr>
</tbody>
</table>

### 1.3.1.1. Methods for staging

**Computed tomography (CT) of the thorax**

CT is the most widely applied staging examination in lung cancer and can define the location, size and anatomical characteristics of a tumour. CT can detect invasion of the tumour into the chest wall or mediastinum but is not reliable in distinguishing between T2 and T3 lesions concerning pleural/chest wall invasion. A 3D reconstruction for virtual bronchoscopy can be done but mucosal abnormalities cannot be visualized. CT has a sensitivity in T (tumour), N (node), M (metastases) and TNM of 68%, 66%, 88% and 46% respectively.115

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PET-CT

When the treatment intention is curative, staging with ¹⁸F-FDG-PET-CT has become standard ¹¹⁶. In one study, Subedi et al showed that PET-CT was a better overall predictor of correct staging for all parts of TNM. For T-staging (PET-CT 64% vs CT 58%), for N-staging (PET-CT 78% vs CT 65%) and for M-staging (PET-CT revealed occult metastases in 16 pat). PET-CT influenced or changed the decision in 41% of the patients. Addition of PET-CT to other evaluation methods, gives a marked improvement in staging of NSCLC. Patients were frequently spared unnecessary treatment, and management was more appropriately targeted. PET permits reduction in the number of thoracotomies performed for non-resectable disease with predicted reduction in the morbidity rate and cost associated with unnecessary interventions ¹¹⁷.

Additional imaging methods for extra thoracic metastases

Typical sites for metastases from lung cancer are the brain, liver, adrenal glands and bone. Routinely a CT of thorax and upper abdomen is performed. A better staging could be achieved with the addition of MRI or CT of the brain, a radio nucleotide bone scanning and a contrast enhanced ultrasound of the liver. In the studies included in the present thesis no further extra thoracic diagnostic procedures was performed if the patient were asymptomatic without any clinical findings. This is in line with the recommendation from a publication of Silvestri et al in 2003 ¹¹⁸. However, today in 2009, PET-CT is considered standard in the diagnostic work up.

Invasive staging

In all patients with a suspected lung malignancy a bronchoscopy is performed. It is central for staging and cytological diagnosis could be achieved with bronchusavalveolar lavage, brushing and endo- or transbronchial needle aspiration. If the tumour is centrally located a direct visualization is possible. If the findings with bronchoscopy reveal no tumour a transbronchial needle aspiration (TBNA) can be done. This procedure is however best suited for central lesions, mediastinal lymphadenopathy or subcarinal nodes.

Transbronchic needle aspiration is an alternative for peripherally located lung tumours not possible to reach with a bronchoscope. The risk of pneumothorax is reported to be 10-30% of patients requiring interventions (catheter for evacuation) ¹⁰²¹⁴. In Karolinska less than 10% of the patients experience a pneumothorax with fine needle aspiration and only half of them need any intervention. Nevertheless, in patients with markedly reduced lung capacity this side-effect could be fatal why strict caution should be taken. There is, however, data showing that a negative transbronchic biopsy turned to be misleading in 30% of patients with a later on diagnosis (surgery or a second biopsy) of malignancy ⁴¹¹²¹². These data contributes, in a way, to the performance of fewer biopsies. Worries about seeding in the needle track is not a big issue anymore and a recent publication with a comparison of over thousand patients who went through biopsy and those who didn’t showed no difference in survival between the two groups ¹¹⁵.

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Mediastinoscopy is performed under general anaesthesia and was earlier standard procedure for mediastinal staging of lymph nodes. In the Stockholm region today, a PET-CT together with TBNA is the first diagnostic procedure. If the result is not conclusive then a mediastinoscopy is considered.

1.3.2. TREATMENT INDICATIONS AND CONSIDERATIONS

All patients are referred to the radiotherapy units via multidisciplinary conferences which include pulmonologists, oncologists, surgeons, pathologists and radiologists. The patients with stage I NSCLC are discussed for surgery as the first treatment option but when judged as inoperable, primarily due to insufficient pulmonary reserve or due to severe cardiovascular disease, SBRT is considered. Some of the patients considered as operable are old and do not want to undergo surgery. If the tumour is technically treatable, the patient is accepted for SBRT.

Is it possible that patients with severe co-existing diseases may not benefit from active oncologic treatment if they only have a small early stage NSCLC? Perhaps they will only experience side effects from the treatment. Two studies examined the survival of untreated inoperable patients with stage I NSCLC. In one study the mean survival time in 19 untreated patients was 17 months and the 2-year survival rate was 20%[124]. In another study of 49 patients with stage I NSCLC the median survival was 14 months[125]. The survival rates from these studies are poorer than seen after any treatment (CRT, SBRT) in inoperable early stage NSCLC, supporting the conclusion that all patients should be offered ablative therapies if possible.

1.3.2.1. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is a classic gene-environment interaction disease where the risk factor is primarily smoking but also high age where an individual is most susceptible of developing COPD[126]. The total burden of inhaled particles and gases over a lifetime contributes to the cumulative response in the lungs. Particles may come from active or passive smoking and environmental sources. This particulate burden is modified by the individual’s nutrition, infections, socioeconomic status, and genes that may increase or decrease the risk. Still tobacco continues to be the most important preventable cause of death worldwide. The recent WHO Report on the Global Tobacco Epidemic predicts that tobacco will kill over 175 million people worldwide between now and 2030[127]. The majority of these deaths will occur in developing countries.

COPD actually comprises two related diseases, chronic bronchitis and emphysema, one rarely occurring without a degree of the other. COPD is characterised by reduced maximal expiratory flow and slow forced emptying of the lungs; features that do not change markedly over several months. Chronic bronchitis is defined clinically by the presence of chronic bronchial secretions, enough to cause expectoration, occurring on most days for a minimum of 3 months of the year for 2 consecutive years. The pathological basis of chronic bronchitis is mucus hypersecretion secondary to hypertrophy of the glandular elements of the bronchial muosa. The limitation in airflow is only minimally reversible with bronchodilators. The pathological definition...
of emphysema involves a condition where there is permanent destructive enlargement of the airspaces distal to the terminal bronchioles without obvious fibrosis. The majority of the patients with stage I NSCLC also suffer from chronic obstructive pulmonary disease (COPD). A mild or median form of COPD is usually not a contraindication for optimal curative treatment but if the COPD is severe or very severe only tumour treatments that are designed to spare as much lung tissue as possible can be recommended. A correct division of COPD in to grade of severity is important in order to present the best treatment alternative (table 4).

Patients with severe COPD (FEV1 50 % or less) have a reduced survival time with an expected 3-year overall survival of about 66-70 %. The GOLD criterion is useful when assessing the risk of complications and death in patients with COPD. However, other risk factors such as the presence of hypoxemia and hypercapnia, a short walk distance in a fixed time, a high degree of dyspnoea and a low body index are also associated with an increased risk of death. A multidimensional 10-points grading system, the Bode index (table 5), that assessed the respiratory and the systemic aspects of COPD was proposed by Celli et al in 2004. Higher scores indicate a higher risk of death. The Bode index is not yet in use when evaluating lung cancer patients but is proposed as a supplement to the GOLD criteria in future pre treatment decisions.

**Table 4. Classification of COPD according to the severity of the disease with the commonly used GOLD criteria:**

<table>
<thead>
<tr>
<th></th>
<th>GOLD I</th>
<th>GOLD II</th>
<th>GOLD III</th>
<th>GOLD IV</th>
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<tbody>
<tr>
<td>FEV1/FVC</td>
<td>&lt; 0.7</td>
<td>&lt; 0.7</td>
<td>&lt; 0.7</td>
<td>&lt; 0.7</td>
</tr>
<tr>
<td>FEV1%</td>
<td>≥ 80%</td>
<td>≥ 50% ≤ 80%</td>
<td>≥ 30% ≤ 50%</td>
<td>&lt; 30%</td>
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The Global initiative for chronic Obstructive Lung Diseases (GOLD) published guidelines for COPD in 2001 (revised in 2004) with classification of the severity of COPD into 4 groups. The categorization was based on the forced expiratory volume in one second (FEV1) divided by forced vital capacity (FVC) as one variable and FEV1 as another variable. Predicted values of FEV1 are obtained from an internally derived linear regression based on height and age in a subgroup of male and female never-smokers. 

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**Bode index**

1. Body mass index (B)
2. Degree of airflow obstruction (O)
3. Functional dyspnoea (D)
4. Exercise capacity (E)
1.3.2.2. Cardiovascular disease

Cardiovascular disease (CVD) is a group term including patients with heart failure, cardiac arrhythmia, stroke, aneurysm, prior heart attacks etc. COPD is associated with a 2 to 3 times higher risk of CVD which is independent of other risk factors. A low FEV1 is a specific predictor of mortality as a result of cardiac causes, even stronger than increased cholesterol: for each 10% reduction of FEV1, CVD induced mortality increases by 28%138. Moreover, the main causes of death among COPD patients are of cardiovascular origin. COPD and CVD have two major risk factors in common - advanced age and tobacco smoking. To predict the outcome of patients with CVD as a group is complicated but the development of different co-morbidity scales like the Charlson comorbidity index (table 6) may contribute to a better classification of the patients with CVD.

1.3.3. SURGERY

Surgery is the standard treatment for early stage NSCLC and lobectomy is considered the standard surgical procedure. Due to the location of the tumour 5-15% of the patients require a bilobectomy and further 4-15% a pneumonectomy140,141. In frail patients who may not tolerate lobectomy, a more limited procedure, i.e. segmentectomy or wedge resection is used. Although data regarding local control is inconsistent142 a meta-analysis on published literature reported comparable survival with both limited resection and lobectomy for stage I lung cancer143. About 20-30% of the patients develop recurrence after surgery despite pre-operative staging using 18F-FDG PET and loco-regional recurrences is reported in 7-12% of the patients103,144. Sixty percent of all recurrences develop within 2 years and only about 10% develop after five years or later. Second primary lung tumours is assumed to occur at a rate of 1-2% per patient and year 138,146. Five- year survival was reported to be 50-70% 138,142 but a large difference within stage I was observed with a 5-year overall survival of 77% for small T1 tumour and only 35% for large T2 tumours 148.

Side effects after surgery is expected and important complications as atrial arrhythmias and prolonged air leak were reported in up to 38% of the patients. Post-surgical 30 day mortality ranged between 1-5% for lobectomy and up to 10% after
right sided pneumonectomy 147. A procedure which may reduce the morbidity associated with open thoracotomy, especially postoperative pain, is the use of video assisted thoracoscopic surgery (VATS). Although VATS has been used since the 1990’s, this procedure was only performed in 10% of patients included in a recent large multi-institutional study 148,149. The safety and efficacy of VATS remains to be confirmed in larger randomized trials.

Surgery is associated with loss of pulmonary function and exercise capacity that ranges from 10 to 40%, depending on the extent of the resection and time elapsed from surgery 150. Respiratory symptoms and pain are important factors affecting quality of life (QoL) after surgery. One study of long term survivors after surgery of lung cancer reported a frequent deterioration in QoL 152. Yet, another study with short term follow up showed no deterioration of QoL at 12 months after lobectomy but for pulmonectomy the initial decline directly after surgery remained at 12 months 153. Post-thoracotomy pain is a frequent symptom, persisting for more than 4 years in approximately 30% of patients 154, and 5% of the patients experience severe and disabling post-thoracotomy pain syndromes 155.

In the preoperative investigation it is necessary to identify patients in whom a lung resection would result in an unacceptable high risk of side-effects and possible death. The investigation should not only contain assessment of postoperative lung function but also a thorough clinical examination, information of weigh loss and cardiac co morbidities. In the preoperative setting lung function tests with dynamic spirometry including FEV1, FVC (forced vital capacity), VC (vital capacity), diffusion capacity (DLCO) and a test of the work capacity are performed. A stair test with measurements of blood gases (PO2, PCO2) before and after work is often done. Parameters directly correlated to morbidity and mortality after surgery is work capacity, FEV1, FVC and increased PCO2.

A preoperative DLCO < 60% implies an increased risk of postoperative complications. As a rule, with a pre operative FEV1 > 2.0L or > 60% of predicted value the patients is expected to tolerate a pulmonectomy and with FEV1 1.2-1.5L or 40% of predicted value a lobectomy should be tolerated. With a calculated postoperative lung function of DLCO > 40% and FEV1 > 0.8-1.0L no pulmonary restriction regarding lobe or pulmonectomy exits. Concerning the work capacity the limit to accept a patient for pulmonectomy is > 80-100W and for lobectomy 55W. A preoperative raise in PPO2 (hyperkapnija), implies a higher postoperative risk. Further risks of surgical complications are; heart attack < 3-6 months before surgery, coronary artery disease, left ventricular failure, arrhythmia, aorta stenosis, obesity, smoking and infection.

With dynamic spirometry a postoperative FEV1 in ml can be calculated according to:

\[ FEV1_{postop} = \left( \frac{b}{19-n} \right) \times FEV1_{preop} + 250 \]

b = number of removed lung segments
n = number of occluded lung segments
19 = the total number of lung segments

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Charlson co morbidity index (CCI) (table 6) could be used to predict long-term outcome after surgery and was in one study shown to be a better predictor of survival than individual co morbid conditions in NSCLC surgery. Patients classified according to the CCI in co morbidity grade: 0, 1-2, 3 or more had a 5-year overall survival of 52%, 48%, 28%, 156,157.

**Table 6. Charlson co morbidity index**

<table>
<thead>
<tr>
<th>Score</th>
<th>Conditions</th>
</tr>
</thead>
</table>
| 1     | Cardiovascular disease (CVD)  
Including: myocardial infarction, CABG, angina  
Congestive heart failure  
Peripheral vascular disease  
Cerebrovascular disease  
Dementia  
Chronic obstructive pulmonary disease (COPD)  
Connective tissue disease  
Ulcer disease  
Mild liver disease  
Diabetes |
| 2     | Hemiplegia  
Moderate to severe renal disease  
Diabetes with end-organ damage  
Any prior solid tumour  
Within 5 year of diagnosis  
Leukaemia  
Lymphoma |
| 3     | Moderate to severe liver disease |
| 6     | Metastatic solid tumour  
AIDS  
Not only HIV positive |

The total equals the score. Example: COPD (1) and CVD (1) = total score (2).
2. AIMS OF THE THESIS

The overall aim of this thesis was to investigate whether stereotactic body radiotherapy (SBRT) could be considered as a safe and potent therapeutic option in medically inoperable patients with stage I non-small cell lung cancer (NSCLC).

The specific aims of the studies were:
- To analyze tumour control, survival and toxicity in a retrospective multicenter material of patients with stage I NSCLC treated with SBRT. (Study I)
- To evaluate treatment related toxicity in a prospective multicenter phase II study of SBRT in patients with stage I NSCLC. (Study II)
- To investigate how co-existing diseases with chronic obstructive pulmonary disease or/and cardiovascular disease relates to the severity of toxicity. (Study II)
- To explore progression free survival, overall- and cancer specific survival, local tumour control, toxicity and performance status in a prospective multicenter phase II study of SBRT in patients with stage I NSCLC. (Study III)
- To use different models for fractionation correction in normal tissue complication probability (NTCP) models and to investigate if SBRT differs from conventionally fractionated radiotherapy (CFRT) regarding response in the lung. (Study IV)
3. MATERIAL AND METHODS

3.1. PATIENT AND TUMOUR CHARACTERISTICS

The study group consisted of 186 medically inoperable patients and 9 patients who refusing to undergo surgery. All patients, included in 2 different studies, had stage I NSCLC and were treated with SBRT from 1996 to 2005.

The first study was a retrospective analysis of 141 patients (56 T1 and 85 T2) treated at four institutions in Sweden and one in Denmark from 1996 to 2003.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non small cell lung cancer stage I: T1–T2 N0 M0</td>
</tr>
<tr>
<td>Medical inoperability or refusal to undergo surgery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing chemo/radiotherapy for other malignancies</td>
</tr>
<tr>
<td>Progressive malignant disease with lung involvement</td>
</tr>
</tbody>
</table>

The median age was 74 years (range 56-90). Seventy two were women and 69 were men. The patients were considered inoperable mainly due to poor lung function (COPD) (55%) or severe cardiovascular disease (CVD) (18%). Since the cause of these diseases is the same, smoking, it was usual that the patient had a combination (COPD+ CVD) (15%). Ten percent had other malignancies and two percent had other compromising diseases. Four percent of the patients were operable but refusing surgery. The median tumour diameter was 37 mm (range 10-90) and the tumors were mainly localized in the periphery of the lung. A morphologic diagnosis was established in 76% with 41% adenocarcinoma, 37% squamous cell carcinoma, 3% bronchoalveolar cells carcinoma and 20% unspecified NSCLC. Risk of fatal pneumothorax rendered biopsy unfeasible in patients with heavily impaired pulmonary function. If no morphology possible to obtain an increase in size with malignant characteristics between the two latest CT scans, with an interval of approximately 3 months, together with exclusion of any evidence of extra pulmonary tumour, was used to set the diagnosis of lung cancer. Radio nucleotide bone scanning, CT of the brain or abdomen and PET were not routinely used to exclude distant metastases. Patient information was retrieved from medical files, x-rays and CT films and from the national registries of death causes.
The second study was a prospective phase II study that included 60 patients with stage I NSCLC treated with SBRT at five institutions in Sweden, one in Denmark and one in Norway from 2003 to 2005. Three patients were not evaluable since two received inadequate radiation doses (according to the protocol) and one was directly lost to follow-up. All analyses were therefore done on 57 patients.

The median age was 75 years (range 59-87) with 31 women and 26 men. Forty patients (70%) had T1 and seventeen patients (30%) had T2 tumours. The median tumour diameter was 25 mm (range 6-50 mm). Of the morphologically verified tumours (67%), 50% were adenocarcinomas, 21% squamous cell carcinomas, 3% large cell carcinomas and 26% unspecified NSCLC. The patients were considered inoperable mainly because of COPD (65%) or CVD (25%). Two patients (3%) were inoperable due to other reasons; one had an advanced joint disease and one had iatrogenic lung fibrosis. Four (7%) patients refused surgery. The baseline mean FEV1% was 64% (range 20-162) in all patients and 50% (range 20-142) in the COPD patients. Karnofsky based median performance status at baseline was 80 (range 70-100).

Inclusion Criteria
- Non small cell lung cancer stage I: T1-2 N0 M0.
- Medically inoperable or refusing surgery.
- Morphologically verified. If morphological diagnosis is unavailable due to high risk associated with diagnostic procedures a CT showing a lesion suggesting lung carcinoma and a subsequent sequence showing increase of that lesion is required.
- SBRT should be technically feasible (i.e. permit the delivery of 15 Gy x 3).
- Life expectancy of ≥12 months.
- Karnofsky performance status ≥70.
- Over 18 years of age at time of inclusion.
- Signed written informed consent obtained.

Exclusion criteria
- Central tumor growth adjacent to trachea, main bronchus or esophagus.
- Previous laser treatment of intra bronchial tumor growth.
- Patients inaccessible for treatment follow up.
- Pregnancy
- Patients with prior malignancies within the last five years (except adequately treated basal cell carcinoma of the skin or in situ carcinoma of the skin or in situ carcinoma of the cervix, surgically cured).

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The primary objective in the prospective study was progression free survival at 36 months and secondary objectives included survival, toxicity, local tumour control, time to progression, safety and quality of life.

The patients included in the prospective study were all required to perform following baseline examinations:

<table>
<thead>
<tr>
<th>Baseline investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray and CT of the thorax and the upper abdomen within 6 weeks before start of SBRT.</td>
</tr>
<tr>
<td>Bronchoscopy.</td>
</tr>
<tr>
<td>Morphological examination of tumour showing the diagnosis of non-small cell lung cancer (biopsy, cytological diagnosis of brush material, bronchoalveolar lavage or sputum during bronchoscopy, Transthoracic fine needle aspiration biopsy).</td>
</tr>
<tr>
<td>Objective lung and heart functions tests with dynamic spirometry including CO-diffusion test (DLCO) and EKG at rest.</td>
</tr>
<tr>
<td>Performance status with Karnofsky performance scale.</td>
</tr>
<tr>
<td>Baseline quality of life assessment using the EORTC QLQ 30 and LC14 formula.</td>
</tr>
<tr>
<td>PET if possible.</td>
</tr>
<tr>
<td>Examination of the lungs, heart, oesophagus and skin according to the toxicity scale common toxicity criteria version 2 (CTC v 2.0).</td>
</tr>
</tbody>
</table>

The primary objective in the prospective study was progression free survival at 36 months and secondary objectives included survival, toxicity, local tumour control, time to progression, safety and quality of life.

The patients included in the prospective study were all required to perform following baseline examinations:

Table 7. Patient and tumour characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Retrospective</th>
<th>Prospective</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of evaluable patients</td>
<td>141</td>
<td>57</td>
</tr>
<tr>
<td>Median age (year) range</td>
<td>74-90</td>
<td>59-87</td>
</tr>
<tr>
<td>Female/male</td>
<td>72/69</td>
<td>31/26</td>
</tr>
<tr>
<td>T1/T2</td>
<td>56/85</td>
<td>40/17</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>44</td>
<td>19</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>39</td>
<td>8</td>
</tr>
<tr>
<td>Bronchial alveolar cells carcinoma</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>ND</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>Inoperable due to: COPD</td>
<td>99</td>
<td>37</td>
</tr>
<tr>
<td>CVD</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Mean tumour volume range</td>
<td>39</td>
<td>16</td>
</tr>
<tr>
<td>cc</td>
<td>2-436</td>
<td>1-51</td>
</tr>
<tr>
<td>Median tumour size range</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>mm</td>
<td>10-90</td>
<td>6-50</td>
</tr>
</tbody>
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<td>25</td>
</tr>
<tr>
<td>mm</td>
<td>10-90</td>
<td>6-50</td>
</tr>
</tbody>
</table>
Assessment of toxicity was done at every follow-up with clinical examination including PS, radiological evaluation with CT and lung function measurement with spirometry at 3, 9 and 18 months post SBRT. Toxicity scoring was performed with the Common Toxicity Criteria version 2.0 (CTC v2.0) [38]. For radiation-related pulmonary fibrosis >90 days post SBRT, the RTOG/EORTC Late Radiation Morbidity Scoring Scheme-Lung was used [39].

In a first report of toxicity (study II) correlated to comorbidity, the patients were divided in groups of COPD and CVD and analyzed separately. The COPD patients were further sub classified into four groups according to the GOLD criteria (see section 1.3.2.1).

Table 8. Classification, according to the GOLD criteria, of the patients included in the prospective study (study II)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>CVD</th>
<th>GOLD I</th>
<th>GOLD II</th>
<th>GOLD III</th>
<th>GOLD IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Female</td>
<td>41</td>
<td>10</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Male</td>
<td>26</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Age, mean</td>
<td>75</td>
<td>60</td>
<td>60</td>
<td>70</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>FEV1%</td>
<td>59-87</td>
<td>62-82</td>
<td>62-82</td>
<td>59-82</td>
<td>62-82</td>
<td>62-71</td>
</tr>
<tr>
<td>Karnofsky</td>
<td>37</td>
<td>9</td>
<td>3</td>
<td>5</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Tumour vol. mean (cc)</td>
<td>16</td>
<td>21</td>
<td>9</td>
<td>12</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Tumour location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right sup</td>
<td>20</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Right inf</td>
<td>8</td>
<td>5</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Left sup</td>
<td>17</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Left inf</td>
<td>8</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>FEV1%</td>
<td>64</td>
<td>97</td>
<td>107</td>
<td>65</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>Karnofsky, median</td>
<td>80</td>
<td>90</td>
<td>70</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Pat. with COPD+CVD</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Three patients did not undergo surgery due to:
Advanced age plus joint disease (2), lung fibrosis (1)
FEV1%: forced expiratory volume in 1 second
Karnofsky: performance status scale graded from 10-100
3.2. SBRT DOSES

All patients were treated with SBRT in the stereotactic body frame (SBF) described in section 2.2.2 treatment procedure. In the retrospective material several different radiation doses was used ranging from 2.4 fractions of 10-20 Gy while in the prospective study all patients where treated with 15 Gy in three fractions prescribed to the 67% isodose at the periphery of the PTV (table 9).

### Table 9. Dose fractionation schemes in the retrospective and prospective study

<table>
<thead>
<tr>
<th>Total dose Gy</th>
<th>Fractions no</th>
<th>BED Gy</th>
<th>Patients no</th>
<th>Patients %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>3</td>
<td>113</td>
<td>80</td>
<td>57</td>
</tr>
<tr>
<td>48</td>
<td>4</td>
<td>106</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>120</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>4</td>
<td>80</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>36</td>
<td>3</td>
<td>79</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
<td>75</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>60</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>3</td>
<td>113</td>
<td>57</td>
<td>100</td>
</tr>
</tbody>
</table>

BED = biologic effective dose

3.3. NTCP MODELLING OF LUNG TOXICITY

In SBRT of lung tumours there is no established relationship between dose-volume parameters such as MLD, V10 etc, and the incidence of clinical radiation pneumonitis (RP2+). In a separate study (study IV) literature data was reviewed and normal tissue complication probability (NTCP) modelling was performed with the Lyman-Kutcher-Burman (LKB) model and parameters for the NTCP model were determined for a lung SBRT data-set using the USC fractionation correction model.

Published data on lung toxicity (RP2+) after CFRT for breast was compiled and compared. All dose data was corrected to a biological effective mean lung dose (MLD), defined as the total lung volume minus the Gross Tumour Volume (GTV). The doses were corrected to 2 Gy/fraction with the LQ-model with an α/β ratio of 3 Gy.

NTCP modelling of toxicity may give an insight into the volume dependence for the radiation response mechanism. Commonly used NTCP models are based on three parameters describing the dose-response curve; first a volume dependence parameter (n) and then two parameters describing the dose-response curve - the steepness (m) and the dose where the probability of the selected response parameter is 50% (D50).

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<td>113</td>
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<td>57</td>
</tr>
<tr>
<td>48</td>
<td>4</td>
<td>106</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>120</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>4</td>
<td>80</td>
<td>18</td>
<td>13</td>
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<tr>
<td>36</td>
<td>3</td>
<td>79</td>
<td>1</td>
<td>0.5</td>
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<tr>
<td>30</td>
<td>2</td>
<td>75</td>
<td>5</td>
<td>4</td>
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<tr>
<td>30</td>
<td>3</td>
<td>60</td>
<td>33</td>
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Dose-volume histograms (DVH) and toxicity data from a subset of 17 patients included in the prospective study, where RP2+ was seen in 10.5% of the patients, was used for the NTCP modelling. Due to the uncertainty of the LQ model for fractionation correction in SBRT, the USC model as suggested by Park et al. as well as the linear quadratic (LQ) model with $\alpha/\beta$ of 3 and 20 was used to correct DVH data to 2 Gy/fraction.

The parameters of the USC model ($D_0$, $n$) and the parameters of the NTCP model ($m$, $n$, $D_{50}$) were determined in a fitting procedure, as described in detail in study IV.

The dose volume dependence in the SBRT data set was controlled by calculating $V_5$, $V_{15}$ and $V_{25}$ from total lung DVHs corrected with the USC model.
4. RESULTS AND DISCUSSION

With a retrospective study there will always be limitations in the interpretation of the results since the information is collected from archived files of radiological material and medical records. Even if our retrospective study included a reasonable large patient cohort and the treatment procedure with SBRT was conformal, no information of such important parameters as performance status (PS) was available. A prospective study was therefore performed with the aim of confirming the results of tumour response, tumour control and survival from the retrospective study and to supplement the information of toxicity and add data on performance status. The median follow-up in the retrospective study (study I) was 33 months (1-107 months) and in the prospective study (study II) 35 months (4-47 months). A first analysis of early toxicity (study II) was done in the prospective study at a median follow-up of 23 months (range 3-42 months). Furthermore a separate NTCP modelling study (study IV) of patients treated at Karolinska University Hospital was performed.

4.1. RESPONSE

Response evaluation is difficult after SBRT since post radiological changes in the lung, pneumonitis, atelectases and fibrosis can mimic tumour progression 95. The tumour itself, as defined by imaging procedures (CT and PET scans), does not always disappear with time even if there is no sign of remaining tumour activity. In general complete response (CR) and partial response (PR) is considered as response but for reasons presented above also stable disease (SD) was included in the response criteria in the present studies. Assessment of response was primarily performed with CT where a PET-CT was only done when a suspicion of tumour progression existed. Response data should therefore be interpreted with some caution.

Radiological examinations were performed at different time points after SBRT (median 16.3 months, range 0.5 - 89.3) in the retrospective study, which is the reason why "best response" is reported (table 10). The rate of CR was similar while SD was more frequent in the retrospective compared to the prospective study. The quality of the radiological examinations will naturally affect the evaluation. Only 4 patients had a local progress at first response examination.

<table>
<thead>
<tr>
<th>Table 10. Best response in the retrospective and the prospective study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
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With a retrospective study there will always be limitations in the interpretation of the results since the information is collected from archived files of radiological material and medical records. Even if our retrospective study included a reasonable large patient cohort and the treatment procedure with SBRT was conformal, no information of such important parameters as performance status (PS) was available. A prospective study was therefore performed with the aim of confirming the results of tumour response, tumour control and survival from the retrospective study and to supplement the information of toxicity and add data on performance status. The median follow-up in the retrospective study (study I) was 33 months (1-107 months) and in the prospective study (study II) 35 months (4-47 months). A first analysis of early toxicity (study II) was done in the prospective study at a median follow-up of 23 months (range 3-42 months). Furthermore a separate NTCP modelling study (study IV) of patients treated at Karolinska University Hospital was performed.

4.1. RESPONSE

Response evaluation is difficult after SBRT since post radiological changes in the lung, pneumonitis, atelectases and fibrosis can mimic tumour progression 95. The tumour itself, as defined by imaging procedures (CT and PET scans), does not always disappear with time even if there is no sign of remaining tumour activity. In general complete response (CR) and partial response (PR) is considered as response but for reasons presented above also stable disease (SD) was included in the response criteria in the present studies. Assessment of response was primarily performed with CT where a PET-CT was only done when a suspicion of tumour progression existed. Response data should therefore be interpreted with some caution.

Radiological examinations were performed at different time points after SBRT (median 16.3 months, range 0.5 - 89.3) in the retrospective study, which is the reason why "best response" is reported (table 10). The rate of CR was similar while SD was more frequent in the retrospective compared to the prospective study. The quality of the radiological examinations will naturally affect the evaluation. Only 4 patients had a local progress at first response examination.
In the prospective study radiological examinations with CT were performed at 6 weeks, 3, 6, 9, 12, 18, 24 and 36 months. During the follow-up period some of the patients died and in figure 6 is response (CR, PR or SD) displayed at different time points given in percent of living patients. In the column called “end of study” all patients are included with the response they had when they died, discontinued the study for other reason or completed the entire study. CR increased steadily over time which is partly represented by the often slow disappearance of the lung lesion after SBRT. Another obvious explanation is that with longer follow-up the chance of CR is increased. However, no cut-off time for optimal response evaluation could be set.

At risk:       57           56           51           49           45           37          33           28          ...
0
10
20
30
40
50
60
70
6 w 3 m 6 m 9 m 12 m 18 m 24 m 36 m End of
study
Percent of the patients
CR
PR
SD

Figure 6. Response rates in percent at every follow-up and at end of study, in relation to number of evaluable patient in the prospective study.

In the prospective study it was also possible to evaluate the response in patients with T1 and T2 tumours and to do a correlation to failure or death in lung cancer. Patients with best response CR had a significantly reduced risk of all failures and death in lung cancer (table 11).

Table 11. Best response and failure in the prospective study

<table>
<thead>
<tr>
<th></th>
<th>T1 n 40</th>
<th>T2 n 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>CR n 16</td>
<td>PR n 18</td>
</tr>
<tr>
<td>Dead</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Dead in LC</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Local failure</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Regional failure</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

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</tr>
<tr>
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<td>1</td>
</tr>
<tr>
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<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>
4.2. LOCAL TUMOUR CONTROL

Sixteen patients (12%) in the retrospective study and 4 patients (7%) in the prospective study developed local failure (table 12). This translates into a crude local tumour control of 88% and 93% respectively. Time to local failure varied from 10-49 months. Only three patients with T1 tumours developed local failure and tumour size was found to be the strongest predictor of failure. In the retrospective study 11 out of 16 of the patients with local failures had tumours located in proximity to, and possible contact with, centrally located risk organs or pleura with subsequent difficulties in including the entire target volume in the high dose area. Yet, there was no correlation between the different radiation doses and local failure. In the prospective study only peripheral tumours were included and four local failures, all in T2 tumours, were found. Possible explanations to these failures could be insufficient dose to larger tumours and somewhat smaller margins between CTV and PTV which indicates a higher risk of target miss. Moreover, the dose-planning CT scans were re-evaluated and no obvious difference in dose distribution between controlled and uncontrolled tumours was seen. Eleven patients (55%) with local failure also had distant metastases and only 7 patients had local failure alone.

Table 12. Local failure

<table>
<thead>
<tr>
<th>T-stage</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Prospective</td>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 7. Local failure according to T-stage in 16 patients included in the retrospective study. Only 3 patients with T1 tumours developed local failure appearing later than 3 years after SBRT. The risk of local failure was strongly connected to T-stage.
The radiation doses used in the present studies proved to be sufficient for small T1 tumours but possible no enough for larger T2 tumours. In relation to this a phase I dose escalation study by McGarry et al showed that local failures primarily occurred with doses lower than 16 Gy x 3 but on the other hand a phase II study of 70 inoperable stage I NSCLC treated with doses as high as 20-22 Gy x 3 still reported on 4 local failures. Nevertheless, a re-evaluation and further analysis of higher doses to T2 tumour seems important.

4.3. REGIONAL FAILURE AND DISTANT METASTASES

Nine (7%) and three (5%) of the patients in the retrospective and the prospective study respectively, had regional failure. Only three of these patients had regional failure alone.

Local control affects survival but the correlation with distant metastases is not entirely clear. Patients with larger tumours had a higher risk of metastatic progression but also patients with small tumours continued to develop distant metastases during follow-up (study I-III). Today PET-CT is routinely used in the diagnostic work-up and for staging of NSCLC. In the present studies, however, only a limited number of patients underwent a PET-CT and thus it could not be excluded that disseminated disease was present already at the onset of SBRT. Distant metastases developed in 44 patients (35 patients in the retrospective and 9 patients in the prospective study) (fig.8). This correlates to a median frequency of 23 % (25% in the retrospective and 16% in the prospective study).

Figure 8. All failures in 195 patients included in the retro- and prospective study

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In the prospective study there was a significant reduced risk of local-, regional and distant failure in patients with T1 compared to T2 tumours (fig. 9). When reclassifying the patients, according to the proposed seventh edition of TNM staging for NSCLC (see section 1.3.1), a further reduced risk was noted in 11 patients with a tumour diameter of 2 cm or less (T1a) where no lung cancer related progression or death was observed.

![Graph showing Time to progression in months](image)

**Figure 9. T-stage and time to progression (local- regional and distant failure) in the prospective study.**

### 4.4. TOXICITY

The general impression from clinical work with SBRT is that the side-effects usually are few and mild and mainly consists of skin rash and development of fibrosis in the high dose area in the lung. In the retrospective study, no evidence of toxicity was found in as many as 60% of the patients. In fourteen patients, grade 3-4 toxicity with thoracic pain, atelectasis, rib fracture, pneumonitis, pneumonia, decreased lung function and decreased PS developed. Most common side effects were skin rash, costal fracture, cough and subclinical pneumonitis or fibrosis. In the retrospective study mainly clinically significant toxicity was recorded in the medical files and when old radiological examinations not were found, the radiologist report, which in many cases did not contain any information on expected post irradiated changes, was used in the analysis. Thus, substantial uncertainties existed in the retrospective collection of toxicity data. This led us to undertake a special effort to assess toxicity during follow-up in the prospective trial and to do a separate study on early toxicity.

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In study II a comparison of how co-morbidities with COPD (with different stages of severity according to the GOLD criteria (see section 1.3.2.1)) and CVD affects the outcome of the SBRT treated patients. The question we wanted to answer was to what extent these patients actually tolerated high radiation doses given with curative intent.

The toxicity study was analyzed at a median follow-up of 23 months (range 3-42 months). At this time 20 (35%) of the included 57 patients had died. To get a clear idea of the toxicity in all patients, the maximum grade for each patient during the follow-up period was therefore reported. Subclinical toxicity (grade 1) occurred in 26% of the patients. Thirty-five percent of the patients presented with grade 2 and 21% with grade 3 toxicity. No grade 4 or 5 toxicity occurred. Only 18% of the patients did not have any toxicity at all (to be compared with 60% in the retrospective study) and in 30% no lung related toxicity was reported.

No patients had pneumonitis graded as ≥ 3 and in only 16% of the patients grade 1 or 2 pneumonitis was noted. This is remarkable low since in other SBRT series almost 100% had grade 1 pneumonitis on CT.

Fibrosis was reported in 38% of the patients with 53% in CVD and 33% in COPD patients, with no sign of aggravation during the observation time.

Pleural effusion (PE) was seen in 23% of the patients, with 47% in CVD and 13% in COPD patients. The incidence of fibrosis and pleural effusion was more common in the CVD patients compared to those with COPD. The size of the groups was small and the study design does not create enough power to look at differences between these groups, so no conclusion could be drawn. However, patients with COPD have a lesser amount of remaining healthy lung tissue susceptible to radiation compared to CVD patients which could partly explain the difference in occurrence of fibrosis. In two separate studies a similar pattern after RT was seen in patients with COPD and emphysema.

Patients with CVD had a relatively worse overall outcome. One explanation may be that the CVD patients in this study had larger tumours and were older but they had better baseline performance status (PS) compared to the patients with COPD.

The most frequent side effect was skin rash which was seen in 19 patients with grade 1 and 4 patients with grade 2 toxicity at six weeks with a dramatically decrease to only 2 patients showing grade 1 skin rash at 3 months.

Twelve patients (21%) developed grade 3 toxicity (dyspnoea (4), pain in thorax (2), fibrosis (2), cough (1), rib fracture (1), pneumonia (1) and fatigue (1)) (table 13). These side effects seemed to appear during the first 12 months with no apparent increase at 18 months. Only 2 of the patients that expired during follow-up had grade 3 toxicity and SBRT induced toxicity was not the cause of death in any of these patients according to death certificates and clinical follow-up.

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In the prospective study objective lung function measurements were done with spirometry and FEV1% was analyzed from baseline to last follow-up. No significant decline in mean FEV1% (the decline was not larger than what is expected in a non-irradiated population with time during the follow-up period) was noted for the whole group of patients. There was, however, a 15.5% decline in the CVD group and a 4% decline in the COPD group. The decline was not increased among patients with the poorest lung function in GOLD IV. In individual patients both an increase and a decrease was seen but there was no correlation with the occurrence of fibrosis, pneumonitis, or dyspnoea.

Performance status (PS) stayed unchanged from baseline to last follow-up in the majority of the patients. The mean PS did not decrease in the COPD group but a slight (11%) decrease was seen in the group of patients with CVD. The CVD patients had a higher inclusion value of PS which could affect the results. Among patients with severe COPD neither dyspnoea nor a decrease in FEV1% affected their PS.

Table 13. The incidence of grade 3-4 toxicity according to CTC v 2.0.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Retrospective</th>
<th>Prospective</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>pneumonitis</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>fibrosis</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>dyspnoea</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>pleural effusion</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>atelectasis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>pneumonia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>pain in thorax</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>cough</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>heart failure</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>rib fracture</td>
<td>2</td>
<td>1</td>
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<td>-</td>
</tr>
<tr>
<td>decreased lung function</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>fatigue</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
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Table 14 shows the reported mean, min and max doses [in one point] to risk organs in the prospective study of 57 patients. No correlation to clinical toxicity according to dose was shown. The ribs received a substantial dose in several patients due to peripheral location of the tumours. With the present follow up (median 35 months) no increase in rib fractures or pain in the thorax was seen in patients with doses in the higher dose interval. The risk of rib fracture seems to be connected to the volume of high dose in the thoracic wall. In a study by Dunlap et al did 50% of patients receiving at dose of 30 Gy in 3-5 fraction, in a volume of > 35 ml of the chest wall, develop rib fracture.102.

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Table 1. Mean, min and max doses to organs at risk in the prospective study.

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Risk organ</th>
<th>Mean dose (Gy)</th>
<th>Min dose (Gy)</th>
<th>Max dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>Oesophagus</td>
<td>11.9</td>
<td>1.4</td>
<td>32.8</td>
</tr>
<tr>
<td>37</td>
<td>Myocardium</td>
<td>10.8</td>
<td>0</td>
<td>51.3</td>
</tr>
<tr>
<td>42</td>
<td>Ribs</td>
<td>52.2</td>
<td>24.6</td>
<td>72.9</td>
</tr>
<tr>
<td>47</td>
<td>Medulla</td>
<td>10.5</td>
<td>0.6</td>
<td>20.3</td>
</tr>
<tr>
<td>39</td>
<td>Stem bronchus</td>
<td>14.0</td>
<td>0</td>
<td>58.7</td>
</tr>
<tr>
<td>41</td>
<td>Trachea</td>
<td>10.4</td>
<td>0.3</td>
<td>66.9</td>
</tr>
</tbody>
</table>

In the final report of the prospective phase II study (median follow-up of 35 months (range 4-47) toxicity was shown to be mild in the majority of the patients with 25% having no pulmonary side-effects. Sixteen patients (28%) experienced grade 3 toxicity and 1 patient grade 4 dyspnoea at 36 months (table 13). The grade 4 patient had received SBRT for a new primary tumour in the contra lateral lung 12 months after the first SBRT. No patient had fatal side effects of the treatment and of the 17 patients with grade 3-4 toxicity, 8 were still alive at 36 months.
4.5. RESULTS OF THE NTCP MODELLING OF LUNG TOXICITY

4.5.1. MEAN LUNG DOSE (MLD) AND INCIDENCE OF PNEUMONITIS IN LITERATURE DATA

The incidence of radiation pneumonitis (RP2+) as a function of mean lung dose (MLD), in the collected literature data of breast, lung cancer and whole lung irradiated patients, is shown in figure 10. The dotted line shows the NTCP calculated with parameters (LKB model n=0.9, m=0.37 D_{50}=30 Gy) used for conventionally fractionated radiotherapy (CFRT). The dash-dotted line shows NTCP fitted to whole lung irradiation data. A dose correlation is seen in both CFRT and whole lung irradiation while no such correlation exists in data collected from SBRT studies.

Figure 10. Plot of how the mean lung dose (MLD) correlated to the incidence of pneumonitis using literature data of patients treated with conventionally fractionated radiotherapy (CFRT) for breast cancer, lung cancer and with whole lung irradiation and patients treated with SBRT for lung tumours.

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4.5.2. MODELLED NTCP

In table 15 is shown the result of the NTCP modelling. The volume parameter \( n \) calculated with USC fractionation correction was equal to 0.68 when NTCP (RP2+) was 10.5%. When controlling the sensitivity of the parameter \( n \) with NTCP assuming an incidence of RP2+ of 5% and 15% the value of \( n \) became 0.84 and 0.62 respectively. The LQ based modelling with \( \alpha/\beta = 3 \) Gy and 20 Gy resulted in \( n = 0.83 \) and \( n = 0.54 \).

<table>
<thead>
<tr>
<th>Fractionation correction</th>
<th>( n )</th>
<th>( m )</th>
<th>( D_{av} ) (Gy)</th>
<th>NTCP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USC</td>
<td>0.68</td>
<td>0.4</td>
<td>30</td>
<td>10.5</td>
</tr>
<tr>
<td>USC</td>
<td>0.84</td>
<td>0.4</td>
<td>30</td>
<td>5.0*</td>
</tr>
<tr>
<td>USC</td>
<td>0.62</td>
<td>0.4</td>
<td>30</td>
<td>15.0*</td>
</tr>
<tr>
<td>LQ3</td>
<td>0.83</td>
<td>0.4</td>
<td>30</td>
<td>10.5</td>
</tr>
<tr>
<td>LQ20</td>
<td>0.54</td>
<td>0.4</td>
<td>30</td>
<td>10.5</td>
</tr>
</tbody>
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* Sensitivity analysis of sensitivty analysis of the parameter \( n \).

Table 15. Values of the volume parameter \( n \) as a result of modelling with different NTCP and fractionation corrections with USC and LQ model.

Sensitivity analysis of \( n \) with USC parameters \( D_0 \) and \( \sigma \) resulted in \( n \) varying from 0.55 to 0.74. This shows that \( n \) is significantly lower for extreme hypofractionation as in SBRT for a wide range of \( \alpha \) and \( \beta \) as compared to what is seen after CFRT in lung and breast cancer.

When LKB parameters was obtained from CFRT with \( n = 0.9, m = 0.37, D_0 = 35.183 \) and the LQ model was used for fractionation correction, the NTCP (RP2+) became 6.2% which significantly underestimated the incidence in the SBRT data subset.

The NTCP modelling of SBRT data resulted in \( n = 0.68 \) which implies a more serial architecture of the functional subunits of the lung compared to reported results of NTCP modelling in CFRT, where \( n = 0.9 \). This implies that low dose volumes contribute less and high dose volumes more to NTCP, as compared to the situation in CFRT. According to these results MLD is not likely to be a relevant parameter to predict lung toxicity in SBRT. However, this is in contrast to the results of a study from Torino where MLD was associated with the incidence of RP2+ (see section 1.2.3.5).

In study IV, the relative lung volume \( V_1 \) and \( V_{52} \) had a somewhat better correlation than \( V_{1}, RP2+ \) but was not conclusive.

A correlation of MLD with pneumonitis in breast cancer, lung cancer and whole lung irradiated patients was shown in the literature data.

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4.5.2. MODELLED NTCP

In table 15 is shown the result of the NTCP modelling. The volume parameter \( n \) calculated with USC fractionation correction was equal to 0.68 when NTCP (RP2+) was 10.5%. When controlling the sensitivity of the parameter \( n \) with NTCP assuming an incidence of RP2+ of 5% and 15% the value of \( n \) became 0.84 and 0.62 respectively. The LQ based modelling with \( \alpha/\beta = 3 \) Gy and 20 Gy resulted in \( n = 0.83 \) and \( n = 0.54 \).

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A correlation of MLD with pneumonitis in breast cancer, lung cancer and whole lung irradiated patients was shown in the literature data.
4.6. SURVIVAL

The majority of the patients in the present studies do not have stage I NSCLC as a separate disease. They have other severe comorbidities making them medically inoperable. In overall survival analyses not only the tumour control but also co-morbidities and all aspects of the patients condition (PS, age, smoking, weight loss) contributes to the result. So, even if the lung cancer is eradicated with SBRT the baseline status according to co-existing diseases will probably be unchanged. Nearly half of the patients died during the follow-up period. Could it be proven that it was not related to SBRT? Do patients with COPD (without lung cancer) really die in 50% of the cases within 3 years? These are adequate questions and here at Karolinska there is an ongoing study where patients with COPD without NSCLC are compared to the patients in the present studies with reference to survival. They are matched with respect to gender, age and FEV1%. Unfortunately there has been very hard to find this control group which is the reason why this study is not completed yet. In four COPD studies, Cote and Celli showed that the expected 3-year overall survival for patients with a FEV1 of 50% or less was 66-70% 129-132. The patients included in the prospective trial had a mean FEV1 of 50% (range 20-92%) in the COPD group and the Kaplan-Meier estimated 3-year overall survival was 60% in this group as well as in the whole patient group. The Kaplan-Meier estimated cancer specific survival was 92% in the COPD group and 88% in the whole patient group. Seven patients (12%) died in lung cancer, 15 patients died of concurrent disease (COPD (9), CVD (6)). 3 patients of other malignancies and in 2 patients the cause of death was unknown. The radiation therapy itself was not confirmed to be deleterious by aggravating the reduced lung capacity, in the present studies, and could not explain the drop in overall survival with time. Instead the presence of COPD and CVD is undoubtedly affecting survival time.

In the retrospective study 65% (91/138) of the patients died during follow-up and among them 36 patients died in lung cancer (according to medical records and death certificates). Seven patients died with loco regional lung cancer present. The 3- and 5-year overall- and cancer specific survival was 52% and 26% and 66% and 40% respectively (table 16). Comparing the survival rates in the retrospective to those in the prospective study the cancer specific survival at 3 years was improved (66% in the retrospective and 88% in the prospective). This could perhaps reflect an improved staging of NSCLC but also demonstrate the importance of close clinical follow-up visits in order to evaluate the severity of co-existing diseases versus the contribution of lung cancer to the cause of death.

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Several studies have related the size of the tumour to the probability of receiving local tumour control after radiotherapy. Local tumour control is a strong predictor for increased overall survival. Neither in the retrospective nor in the prospective study did we observe any difference in overall- or cancer specific survival between patients with T1 and T2 tumours (fig. 11).

A correct classification and staging of lung cancer affects the outcome of the treatment and in the revised and recently proposed new TNM system for NSCLC a sub classification of T1 and T2 is suggested due to large differences in survival noted according to tumour size (see section 1.3.1). However, in the studies reported here no survival gain was seen for patients with small tumours in the new TNM system classified as T1a, likely explained by the frequent deaths of other causes than lung cancer among the patients.

Figure 11. Overall- and lung cancer specific survival according to T-stage in the prospective study.

In the retrospective study the SBRT doses were delivered with several different dose regimens and total doses, which made it possible to analyse outcome in correlation to biologic effective dose (BED). In this analysis, the cut-off dose was set at BED = 100 Gy, according to results from Onishi et al where patients who received a total dose lower than 100 Gy in BED had inferior local control and survival compared to those who received a total dose of 100 Gy or more. The results showed a difference in

### Table 16. Overall- and cancer specific survival in the retro- and prospective study

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall survival/Cancer specific survival (%)</th>
<th>Median follow-up months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
<td>2 year</td>
</tr>
<tr>
<td>Retrospective</td>
<td>84/71</td>
<td>64/79</td>
</tr>
<tr>
<td>Prospective</td>
<td>86/93</td>
<td>65/88</td>
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</tbody>
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survival but not in local control between the two chosen dose levels. This was somewhat unexpected and became further surprising when doing a sub analysis of tumour size and total doses. An overrepresentation of T2 tumours was found among patients treated with BED $< 100$ Gy. The better survival in the high dose compared to the low dose group could indeed also be explained by the increased rate of T2 tumours in the low dose group.

With SBRT, unlike surgery, of a lung lesion no pathological anatomical diagnosis (PAD) will be presented after the treatment. It is therefore of outmost importance that the diagnosis of lung cancer is as thoroughly confirmed as possible (see section 1.3.2). Both in the retrospective and the prospective study about a third of the tumours were not morphologically verified and the diagnosis in these cases were in the retrospective study mainly set with CT while a PET-CT was used in majority of these cases in the prospective study. To control for morphology, subset analyses concerning local and regional control, occurrence of distant metastases and overall- and cancer specific survival were done. Not in any of these analyses were a significant difference found between patients with and without morphologic verified tumours.

Fakiris et al recently reported the results from a prospective phase II study of 70 SBRT treated medically inoperable stage I NSCLC patients with a median follow-up of 50.2 months \(^{116}\). In this study was SBRT delivered with doses of 20-22 Gy x 3, prescribed to the 80% isodose line. The local tumour control was high and only 4 patients relapsed. Distant metastases were only seen in 8% and 13% in T1 and T2 tumours respectively. Three year overall survival was 43% and cancer specific survival 82%. Clinical toxicity for peripheral tumours was limited. All tumours in this study were histologically verified and the patients were staged with PET-CT. The SBRT doses were higher in this study compared to the doses used in the studies included in the thesis. Yet, the results of local control and survival are quite similar.
5. CONCLUSION AND FUTURE POSSIBILITIES

The aim of the present thesis was to explore the validity of SBRT in patients with medically inoperable stage I NSCLC. Two studies, one retrospective and one prospective, showed similar excellent results with respect to local tumour control. In both studies regional failure was uncommon despite that no treatment to mediastinal nodes was given. SBRT was well tolerated with only limited toxicity even in patients with severely reduced pulmonary function. No fatal toxicities were recorded and no significant decrease in pulmonary function, as earlier suspected, was shown. Regarding optimal dose to the tumour, the studies were not able to deliver a definitive answer, as they were not designed to study this particular subject. It is possible that T2 tumours require a higher dose to be controlled with SBRT which is why a prospective randomized clinical trial addressing this issue is needed. It is also important to consider the addition of systemic treatment to SBRT in patients with larger tumours, with increased risk of failure, similar to the attitude in surgery.

The promising data of both these studies now supports the ongoing randomized phase II study (SPACE) comparing SBRT with CFRT for stage I NSCLC. This is a collaborative study and performed at the Nordic SBRT centres. To our knowledge no similar study has been published and these two RT regimes have until now not been compared to each other. The result of the SPACE study will eventually provide information on whether SBRT should be considered as standard treatment in future for all medically inoperable early stage NSCLC.

If the lung tissue reacts differently after highly hypofractionated radiotherapy, compared to conventionally fractionated treatments, as suggested by the NTCP modelling in the present study, then the dosimetric predictors of clinical pneumonitis following SBRT might also differ, as the high dose components would be most relevant. However, further studies addressing this issue are warranted.

The rate of local tumour control after SBRT is comparable to results obtained with surgery but the overall survival is undoubtedly inferior after SBRT. Not to forget, operable patients differ substantially in medical status from inoperable patients receiving SBRT. The non-invasive character of SBRT and the limited toxicity post treatment, opens up for a comparison of SBRT with surgery for operable stage I NSCLC. One phase II study of SBRT for operable stage I NSCLC in Japan and one randomized phase III study between surgery and SBRT in the Netherlands are already ongoing.

Mainly peripheral tumours were included in the present studies. Centrally located tumours in the lung have to a lesser extent been treated with SBRT due to risk for increased toxicity in organs at risk (OAR) exemplified by the main bronchus, oesophagus, heart or trachea. Patients with centrally located NSCLC are usually considered technically inoperable and present a challenge also for curative radiation treatments, since the OAR will predominantly be located within the high dose area of the radiation field. However, using small fields, like with SBRT, dose escalation is
possible with careful monitoring of severe toxicity. A phase I dose-escalation study with the aim to determine maximal tolerated dose (MTD) for critical structures in the centre of the thorax was recently opened at the Nordic SBRT centres. Hopefully, this study will not only contribute to improve treatment strategies for centrally located early stage NSCLC but also help to further develop SBRT and define its role in treatments of more advanced tumours. SBRT could preferably be used in combination with CRT to boost the total dose to residual tumours or in combination with chemotherapy to reduce the tumour burden.

In recent years there have been some improvements with pharmaceutical treatment of stage IV NSCLC, with an increased median survival of about two months. Yet, there is a subgroup of stage IV patients with only a few detectable metastases, oligometastases, who have better outcome. The tumour burden itself is probably decisive for survival time. To further prolong the survival time in these selected patients, “down staging” by removing or sterilizing the metastases may be a novel focus for the use of SBRT. A randomized phase II study where SBRT precedes conventional chemotherapy, in the experimental arm, in patients with stage IV oligometastatic disease is about to start Karolinska. If this study shows a substantial benefit in overall survival for the combined arm, it will be extended to a phase III setting.

SBRT is a promising treatment technique with tolerable side effects, even in frail patients, and an excellent alternative to surgery. The future extent of using this technique will depend on the results from several ongoing SBRT studies in Europe, Japan and in USA. With the experience from the studies included in this thesis, use of SBRT for medically inoperable patients with NSCLC is considered safe and recommended on the basis of the favourable treatment results.
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for a pleasant and fruitful teamwork that hopefully will continue in the future

Professor Rolf Lewensohn, my main supervisor, for providing an interesting and exiting research environment and for being such an inspiring spirit with a never fading source of energy and curiosity in new projects

PhD Signe Friesland, my co supervisor and friend, for your devotion, competence and encouraging manner in the clinical work in mixture with a party soul that under no circumstances misses a chance to invite friends and colleagues to magnificent dinners with exquisite champagne

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Boel Hedlund-Svedmyr and Anders Carlsson, for your invaluable effort in organizing the practical things around the SBRT patients

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Finally I want to thank my fantastic and lovely family, Christian, Fanny, Clara, Andrea and Adam. You are the sunshine of my life and nothing is more important to me than your happiness. Your understanding and support carried me all the way through the work with this thesis.

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Lotta Fredholm, for being a fantastic listener and the cleverest person I know.

Leif, my father, for your courage and ability to look at the bright side of life.

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