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STEREOTACTIC BODY RADIATION THERAPY OF PRIMARY LUNG CANCER AND METASTASES

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I dedicate this thesis to my family, for the joy in everyday life.

...”Kärlek
som är att vakna tillsammans
och möta den blåögda morgonen
att utbyta leenden som värmer
och värnar och den nya dagens framtid
att på resan genom dagen
vila tillsammans på klockslagens små väntstationer
och intaga gemensamma måltider
upplysta av lingonsyltens röda glädje”...

Ur Den dagliga kärleken av Maria Wine

ABSTRACT

Stereotactic body radiation therapy (SBRT) has been assessed by both retrospective and prospective studies showing excellent treatment outcome with acceptable toxicity and high grade of local control. However, late presenting effects as well as further evaluating toxic effects in relation to dose-volume parameters at high-fraction doses and clinical characteristics is of the utmost importance in order to further develop the clinical application of this method.

Study I is a retrospective study of 29 patients (32 lesions) who were treated between 1994 and 2004 with reirradiation with SBRT of a previously treated SBRT-lung target. Reirradiation was defined as >50% overlap of the previously treated target. The primary aim was to evaluate toxicity. Serious toxicity was scored in 11 patients, with the toxic effects being lethal for three patients. Noted risk factors for serious toxicity were central location, large CTV and shorter time between the first treatment and the reirradiation. As concluded from the analysis, reirradiation of a peripherally located lung target is feasible, whereas careful consideration should be taken before reirradiating a centrally located target.

In **study II**, we reported on an extended follow-up of a prospectively collected patient cohort with medically inoperable stage I non-small cell lung cancer (NSCLC) treated curatively with SBRT, 15Gyx3. Between 2003 and 2005, 57 patients were included in this study. Long-term follow-up aimed to evaluate late presenting (def. >36 months) effects and toxicity. Five-year-local control and overall survival were 79% and 30% respectively. Three patients had late presenting grade 3 toxicity possibly attributed to their treatment. In conclusion, long-term results of SBRT are excellent and support the further use of SBRT for medically inoperable cases, the shorter survival however, is a limitation, possibly hiding late presenting effects.

Study III is a retrospective study of SBRT-treated adrenal metastases, whose objective was an evaluation of local control and toxicity. Fifty-eight patients with 62 adrenal metastases from various origins were treated between 1999 and 2013 and are included in this analysis. The median prescribed BED_{10} was 80Gy (24-113). Two-year local control rate (based on 60 evaluable tumors) was 87% and grade 3-4 toxicity occurred in 12% of the patients, the majority emanating from gastrointestinal organs. Treating adrenal metastases could render a high grade of local control, which has to be balanced against the risk of toxicity. The clinical challenge is to select the patients truly benefiting from the treatment with disease control and long-term survival.

In **study IV**, 57 patients with 61 SBRT-treated apically located lung tumors, defined as the center of the tumor located above the aortic arch, were retrospectively collected. Here the primary aim was to evaluate radiation induced brachial plexopathy (RIBP). Seven patients presented grade 2-3 RIBP; 3 suffering from sensory/motor deficit and 4 from isolated pain. A normal tissue complication probability (NTCP) model was fitted to the data, the $BED_{3,max}$ NTCP-model did show the best fit. As concluded from this analysis, the brachial plexus has to be considered as a risk organ and a dose-constraint of $D_{max} \leq 30$Gy to the plexus for a three-fraction treatment may be advisable.

LIST OF SCIENTIFIC PAPERS

I. Peulen H, Karlsson K, LINDBERG K, Tullgren O, Baumann P, Lax I, Lewensohn R, Wersäll P. Toxicity after reirradiation of pulmonary tumours with steretactic body radiotherapy. Radiotherapy and Oncology, 2011, volume 101, pp 260-266

II. LINDBERG K, Nyman J, Riesenfeld Källskog V, Hoyer M, Lund JÅ, Lax I, Wersäll P, Karlsson K, Friesland S, Lewensohn R. Long-term results of a prospective phase II trial of medically inoperable stage I NSCLC treated with SBRT – the Nordic experience. Acta Oncologica, 2015. Early online:1-9

III. LINDBERG K, Grozman V, Haasbeek C, Westman G, Lax I, Wersäll P, Andersson A, Lewensohn R. Stereotactic body radiation therapy of adrenal gland metastases – results of a multicenter retrospective analysis of 60 tumor lesions. In manuscript.

IV. LINDBERG K, Grozman V, Lindberg S, Onjukka E, Lax I, Lewensohn R, Wersäll P. Radiation induced brachial plexus toxicity after SBRT of apically located lung lesions. In manuscript.

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LIST OF ABBREVIATIONS

^{18}FDG-PET-CT	18-fluorodeoxyglucose positron emission tomography
4D-CT	four-dimensional CT
ACTH	adrenocorticotropic hormone
ADCA	adenocarcinoma
AE	adverse event
AUC	area under the curve
BED_3	biologically equivalent dose using α/β 3Gy
BED_{10}	biologically equivalent dose using α/β 10Gy
BMI	body mass index
CBCT	cone beam CT
cc	cubic centimeter
CCI	charlson comorbidity index
CFRT	conventionally fractionated radiotherapy
COPD	chronic obstructive pulmonary disease
CRC	colorectal carcinoma
CSS	cancer specific survival
CT	computer tomography
CTCAE	common terminology criteria for adverse events
CTV	clinical target volume
CVD	cardiovascular disease
d	fraction dose
D	total dose
Dig I-V	fingers one to five
DLCO	carbon monoxide diffusion capacity
DM	distant metastases
ΔT	time between first radiation and first re-irradiationd
DVH	dose volume histogram
EBUS	endobronchial ultrasound
EUS	esophageal ultrasound
FEV1	forced expiratory volume in one second
FEV1%	forced expiratory volume in one second, % of predicted
FSU	functional subunit
FU	follow-up
D_{Xcc}	dose to Xcc of the lung
GI-OAR	gastrointestinal risk organ
GTV	gross tumor volume
Gy	Gray
HU	hounsfield unit
IGTV	internal gross tumor volume
KM-analysis	Kaplan-Meier analysis
LC	local control
LF	local failure
LQ-model	linear quadratic model
MLC	multileaf collimator

MLD	mean lung dose
MM	malignant melanoma
MRI	magnetic resonance imaging
N.A	not applicable
N.S	not stipulated
NSCLC	non-small cell lung cancer
NTCP-model	normal tissue complication probability model
OAR	organ at risk
OS	overall survival
PFT	pulmonary function test
PS	performance status
PTS	patients
PTV	planning target volume
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RIBP	radiation induced brachial plexopathy
RC	regional control
RF	regional failure
ROC curve	receiver operating characteristic curve
RTOG	radiation therapy oncology group
SCC	squamous cell carcinoma
SCLC	small cell lung cancer
SBF	stereotactic body frame
SBRT	stereotactic body radiation therapy
SFED	single fraction equivalent dose
TD5/5	the probability of 5% complication within 5 years from treatment
TNM-system	tumor-, nodes- and metastases system
USC-model	universal survival curve model
VEGFi	vascular endothelial growth factor inhibitors
VMAT	volumetric modulated arc therapy
V_X	volume of the lung receiving > X Gy
WHO	World Health Organization

1 INTRODUCTION

Stereotactic Body Radiation Thearpy (SBRT) is a radiation treatment technique, delivering ablative doses to the tumor with very high precision while minimizing the dose to the surrounding normal tissue. This method has spread throughout the world, presenting local control rates of >90% and limited side effects. SBRT is today the standard treatment for patients with medically inoperable stage I non-small cell lung cancer (NSCLC) and is also being used widely in the metastatic setting for various metastatic sites and histologies.

SBRT was developed in the 1990s and towards the end of that decade retrospective analyses in Sweden[1] and Japan[2] have presented promising results for this technique. The analyses were however compromised with the limitations of retrospective studies as well as limitations of heterogeneity of the patient materials and different treatment techniques in use at the various centers. Thus, there was a need for further evaluation of the method to gain scientifically higher levels of evidence. Another issue was the radio-biologically founded hesitation for adapting the method with respect to late presenting toxicity from large-fraction doses. Prospective trials were designed to properly evaluate treatment related toxicity and tumor effects; one of the first being a dose-escalation study[3] conducted in USA by one of the pioneers of this method, Robert Timmerman. This dose escalation study, had delivered extremely high biological doses with acceptable toxicity, which formed the basis for further trials, aiming to evaluate toxicity and efficacy[4]. It soon became apparent that SBRT of peripherally located tumors gained further support whereas treating centrally located lung tumors was afflicted with risk[4]. In 2008 and 2009 the Nordic SBRT-study group published the clinical results from one of the first phase II trials on the method for stage I NSCLC[5,6]. The results from this trial have been of utmost importance in establishing this method in order to treat early stage NSCLC and a long-term follow-up of the included patients is presented in this thesis.

Although SBRT has both few and mildly reported side effects, data is limited on dose tolerance levels for risk organs using these high fractions doses. Many of the commonly used dose constraints in SBRT are direct extrapolations from conventionally fractionated radiotherapy (CFRT) and uncertainty prevails whether these constraints are valid for high-fraction-regimens. Thoroughly addressing toxicity from SBRT-treatments and correlate the presented symptoms to dose-volumetric and clinical data is of major importance to further develop the clinical implications of the technique. This thesis, with focus on toxic effects of SBRT, addresses toxicity in the reirradiation setting (study I), in the setting of SBRT of adrenal metastases (study III) and in the setting of apically located lung lesions focusing on radiation induced brachial plexopathy (study IV). It also presents an analysis of long-term effects of SBRT (study II), with long-term follow-up of a prospectively collected patient cohort.

1.1 STEREOTACTIC BODY RADIATION THERAPY

1.1.1 Basic principles

Stereotactic Body Radiation Therapy (SBRT) was developed at Karolinska University Hospital in the 1990s with the radiosurgical concept used in gamma-knife treatment as a prototype. The principles of radiosurgery were developed in the 1950s by the neurosurgeon Lars Leksell who constructed a frame-based method to treat intracranial lesions stereotactically with high-single fraction absorbed doses. Inspired by the results of the gamma-knife, the pioneering work of the physician Henrik Blomgren and physicist Ingmar Lax led to the invention of extra-cranial stereotactic radiation therapy. One of the obstacles for applying high-precision radiotherapy outside the scull was intra-corporal motion of the target, a dilemma that was overcome with the invention of the stereotactic body frame (SBF). In the SBF, the patient is immobilized in a rigid position, minimizing tumor movement and allowing for tumor positioning in a 3-D-coordinate system[7] (fig 1.3). SBRT was first tested on heavily metastasized patients with few treatment options, but its promising results[1] led to the broadening of the indications, eventually resulting in a major improvement in cancer therapy for patients with medically inoperable early stage NSCLC who now could be offered a treatment with a higher chance of a cure.

The basic principles of SBRT are presented in figure 1.1-1.4.

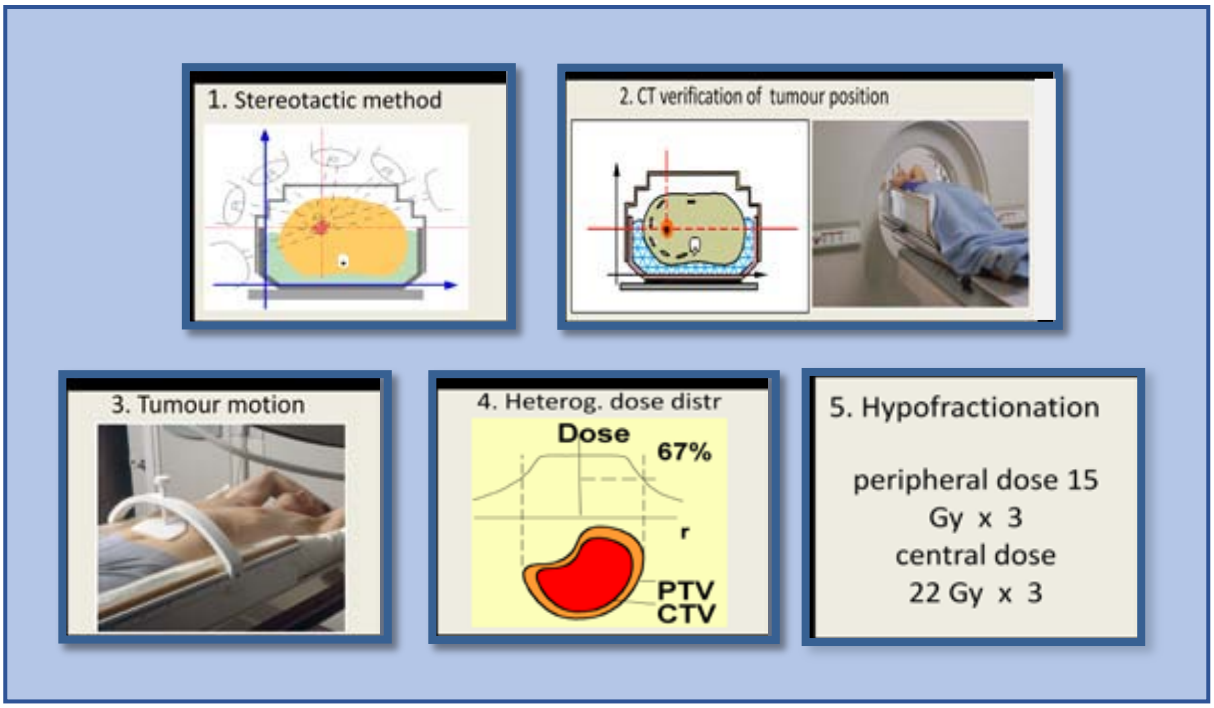


Figure 1: Basic principles of SBRT; 1) The target is localized in a 3-D-coordinate system; 2)Prior to treatment, the tumor position is verified by a verification-CT; 3) The patient is immobilized in the SBF +/- abdominal compression to reduce tumor motions, 4)The dose is prescribed to the 67% iso-dose line encompassing the PTV, resulting in a heterogeneous dose distribution within the target with the central parts of the target receiving ~150% of the prescribed dose, 5) Hypofractionation with a few high-fraction doses resulting in biological equivalent doses (BED) of >100 Gy. (By permission of Ingmar Lax).

1.1.2 The SBRT-technique from the 1990s till today

The fundamental principles of SBRT are shown in figure 1.1-1.4. Practically, before the dose-planning-CT, the patient is fixed with the arms positioned above the head in the SBF with a vacuum-pillow and abdominal compression if the tumor movements are large. The dose-planning-CT is then performed and used for the delineation of the target and relevant risk organs (OAR). The clinical target volume (CTV) comprises the gross tumor volume (GTV) with its diffuse growth at the borders. The planning target volume (PTV) is then created by adding a margin of 5-10 mm to the CTV to account for set-up-errors and breathing motions. The dose is prescribed to about the 67% isodose line encompassing the periphery of the PTV. This creates an inhomogeneous dose distribution with the central parts of the target receiving approximately 150% of the prescribed dose and a rapid dose-fall-off outside the target thus minimizing its dose to normal tissue. The treatment is usually delivered with 6 MV energy that use 5-10 coplanar beams and render a very sharp dose-gradient in the longitudinal plane.

Table I Development of SBRT over time at Karolinska University Hospital

Characteristics	1991-2009	≥2009
Prescription isodose (%)	~67%	
Fixation	Stereotactic body frame	
Dose delivery	Static beams	Static beams/**VMAT (2011)**
Photon energy	6 MV	
No. of beams	5-7 beams	5-7 beams/2-4 arcs
Geometrical verification	CT-verification	**CBCT (2009)**
CTV (definition)	Tumor	
Tumor margin	Long ≥10mm Trans ≥5mm	Individual if large breathing amplitudes
Tumor movement assessment	Diaphragm/tumor movement w. fluoroscopy	**Tumor movement w. 4D-CT (2011)**

VMAT: volumetric modulated arc therapy. CBCT: cone-beam computer tomography. 4D-CT: four-dimensional CT. MV: mega volt.

More recently, along with technical advances in radiotherapy and imaging, the SBRT-method has been refined (table I). Initially, tumor motion during the breathing cycle was assessed by fluoroscopy whereas a 4D-CT scan performed at dose-planning has been in-use since 2011. This allows for a more accurate estimation of tumor movement and the possibility to create individual margins for patients with large breathing motions. Furthermore, image guidance of tumor position with online cone-beam CT (CBCT) directly before each fraction is now performed, allowing for correction of the tumor position in three dimensions with the patient staying in the treatment position. Moreover, dose-calculation algorithms have improved over

time to increase their accuracy of anticipated dose distribution. The introduction of volumetric modulated arc therapy (VMAT) in which the dose is delivered while the gantry rotates in an arc around the patient at the same time as the multileaf collimator (MLC) are modulating the beam configuration and dynamically distribute the dose to the target. VMAT treatments (instead of static fields) are above all used for complicated treatments with targets in close relation to risk organs and allow a better shaping of the dose distribution, aiming to avoid dose to OAR and increase the coverage of dose in the target area. Technique improvements at other centers include gating[8], tumor tracking[8] and the use of an internal target volume (ITV)[9] to mention a few. Here one clinical question of interest though is to what extent the technical progress has led to any improvement in clinical outcomes.

1.2 EARLY STAGE NSCLC

Lung cancer is one of the major cancer diagnoses in the world and the number one cancer related cause of death. The incidence is about 1.8 million cases per year in the world[10] and 3600 cases per year in Sweden[11]. In Sweden, 5-year-survival for all stages is approximately 13-19%[11]. Unfavorable prognostic factors (apart from tumor stage) are male gender[12], high age[11], history of smoking[12] and high performance status (PS)[12]. Lung cancer is divided in small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the latter standing for approximately 80% of all cases. Of these patients, ~65% present in an advanced or metastasized state already at diagnosis and only ~25% have stage I disease[13] and are potential candidates for surgery if fit for that. In this thesis early stage NSCLC, defined as stage I, is addressed specifically in study II and the following chapter will be a discussion of the basic principles of classification, staging, diagnostic work-up and treatment of stage I NSCLC.

1.2.1 Classification and staging

NSCLC is histologically classified into a variety of different tumor types, the two most common being squamous cell carcinoma (SCC) and adenocarcinoma (ADCA). Both types are associated with cigarette smoking[14] and more recent data show ADCA has increased relatively to SCC[15]. Special forms of lung cancer, driven by targetable mutations (for example in the EGFR-complex or by an EML-ALK-translocation) may also be identified but do not alter the treatment for early stage disease.

Except for histology, lung cancer is staged according to the TNM-system which outlines the extent of the disease; T describing the primary tumor, N the lymph nodes and M the occurrence of distant metastases. The TNM-classification[16] is the basis for further classifying the disease into a stage between I-IV. Stage I comprise tumors $\leq$50mm with no nodal involvement or distant metastases.

1.2.2 Diagnostic work-up for early stage NSCLC

If primary NSCLC is suspected, the patient is referred to the Respiratory medicine clinic, which is responsible for the investigation of a suspected lung cancer. The main aims with the investigation are to verify the malignancy of the lesion, to determine the extent of the spread

of the disease and, in collaboration with oncologists and thoracic surgeons, to determine the suitable treatment for the patient.

First, verification of the malignancy of the lesion is done by bronchoscopy, by which the airways are examined visually and by cytological and/or histological sampling. Trans-thoracic needle biopsy may also give cytological/histological confirmation of the suspected malignancy but is affected by a risk for iatrogenic pneumothorax. Radiologically, in addition to a CT of the thorax and upper abdomen, an ^{18}F-FDG-PET-CT is performed. This examination serves to map the extent of the disease and, in cases where there is no histopathological verification; a PET-CT in combination with tumor growth over time may serve as a diagnostic tool for lung cancer. Second, lymph nodes suspected for metastatic involvement may be further examined by fine needle guided endobronchial ultrasound (EBUS), fine needle guided esophageal ultrasound (EUS) or mediastinoscopy.

Apart from verifying the malignancy and the localized stage of the disease, the general status of the patient has to be judged before deciding on the proper treatment of the patient. Lung cancer mainly affects the elderly and many patients also have had a significant smoking history[12]. Such patients therefore often have further complications from other diseases making them unfit for surgery which is the treatment of choice for early stage NSCLC. There are various approaches to decide whether or not a patient is fit to undergo surgery, depending on praxis in various countries and at a variety of centers. Medically inoperability is often very clearly defined in material from the USA for example as described in a large prospective RTOG-trial, where standards for inoperability is pretreatment forced expiratory volume in one second (FEV1) <40% than predicted; post treatment FEV1<30% than predicted; carbon monoxide diffusion capacity (DLCO) <40% than predicted; baseline hypoxemia or hypercapnia; severe pulmonary hypertension; diabetes mellitus with end-organ damage; severe cerebral, cardiovascular or peripheral vascular disease; or severe chronic heart disease[17].

1.2.3 Treatment of early stage NSCLC

The treatment is decided at a multidisciplinary tumor board conference where pneumonologists, thoracic surgeons, oncologists, pathologists, radiologists and nurses participate. The standard treatment for early stage NSCLC is surgery, the type and extent of surgery depending on the anatomical localization of the tumor. A standard form of treatment is lobectomy but sub-lobar resection may also be performed in cases of poor pulmonary function or medical impairment. Generally, for stage I NSCLC, 7%[18] of the patients relapse loco-regionally after surgery and 5-year-overall survival is about 66-75%[18,19]. This type of surgery may however affect the frequency of relapse; in a randomized trial comparing lobectomy and sub-lobar resection, loco-regional recurrence occurred in 7% of the patients undergoing lobectomy versus 17% of the patients undergoing sub-lobar resection[20] and recent results from a metaanalysis comparing segmentectomy and lobectomy showed comparable rates of local recurrence for the modalities, overall- and recurrence free survival being inferior though for patients treated with segmentectomy[21]. Patients medically unfit to undergo

surgical treatment are then referred to radiotherapy, which today is delivered as SBRT. Currently adjuvant chemotherapy after surgery is offered to patients with stage II and selected cases with stage IB, rendering an absolute gain in overall survival of 5% at 5 years.

At present, there are no results from randomized trials comparing SBRT and surgery for early stage NSCLC, since attempted randomized trials have closed prematurely due to poor patient accrual. Reports from observational studies comparing the modalities do exist[22-28]. In terms of local control, SBRT appeared to be superior[23] or comparable to sub-lobar resection[22,24] whereas comparison of local or loco-regional control between lobectomy and SBRT has shown results favoring either of the methods[22,28] or having comparable results[25]. Patient undergoing SBRT are often in poorer health and older as compared to those undergoing surgery. Some studies try to overcome this issue by using matched analyses – a method to compare two groups in an observational study by creating similar baseline characteristics, thereby overcoming bias in the material. Medical impairment and old age have to be taken into consideration when evaluating overall survival (OS). Non-matched analyses show inferior OS for SBRT-treated patients[23,25] whereas analyses matching patients treated with surgery and SBRT, show non-statistically significant differences[24,26,27]. When evaluating cancer specific survival (CSS), the methods seem to be comparable[23,24,27].

Regardless of the outcome from the treatments, there are practical differences between the methods that should be considered. Surgery might lead to upstaging of the disease leading to adjuvant chemotherapy to some of the surgically treated patients[25] , which is not the case for SBRT-treated patients. The definition of local recurrence often differ in surgical and SBRT-materials which should be taken into consideration when comparing reports on these methods. Lastly, current studies comparing surgery and SBRT show heterogeneity in the cohorts both between different SBRT-regimens and the types of surgery[22,25-27].

1.3 SBRT IN THE CLINICAL SETTING

1.3.1 SBRT of medically inoperable early stage NSCLC

Historically, patients with stage I NSCLC unfit to undergo surgical treatment have been referred to conventional radiotherapy, delivered with small fractional doses over several weeks and large margins around the tumor. Tumoricidal doses could often not be delivered with respect to normal tissue tolerance from OAR in the vicinity. These conditions led to decreased rates of local control. Since local control is linked to long-term survival also decreased survival was noted with estimated rates at 3 years for OS and CSS of only 34%±9% and 39%±10% respectively[29], clearly inferior to those being reported from surgery. A few patients could not be treated at all, due to physical impairment, and were followed-up by observation having a dismal prognosis[27,30]. The technique of SBRT allows small margins to normal tissue and the use of a few large-fraction doses, biologically corresponding >150% of dose delivered when using CFRT. As concluded from short-term follow-up of SBRT of

primary early stage NSCLC, SBRT had a high rate of local control, limited side effects and was convenient for patients. Survival has, however, been limited, probably due to a negative selection bias of patients with inter-current diseases. This technique today is standard treatment for medically inoperable early stage NSCLC [31].

Outcome of SBRT of medically inoperable NSCLC addressed in prospective trials[6,32-34] and in large registry based analyses[35,36] has shown local control, regional control and distant control rates of 88-92%,86-91% and 79-87% respectively at 3-5 years[6,32,35,36] (table II). However, data on long-term follow-up is scarce, partly because the technique is young, partly because OS i.e. including all causes of death is low. In comparison to the results after surgery and conventionally fractionated radiotherapy, SBRT is a viable option for medically inoperable patients[24,27], but further evaluation with long-term follow-up is of utmost importance to understand the occurrence of late presenting effects such as late presenting toxicity and relapses.

Table II Overview of results from prospective trials and large cohort studies

Study	**Pts**	**Median-FU**	**LC**	**OS/ CSS**	**Toxicity ≥ G3**
	n	*months/yrs*	*rate*	*rate*	*% of the pts*
Prospective studies					
Fakiris 2009[32]	70	50	88% (3yrs)	43%/82% (3 yrs)	16%
Timmerman 2014[34]	55	4 (yrs)	93% (5 yrs)	40%/N.S (5 yrs)	31%
Matsuo 2010[37]	101	31	87% (5 yrs)	47%/N.S (5 yrs)	3% ≥ G3 pneumonitis
Baumann 2009[6]*	57	35	92% (3 yrs)	60%/88% (3yrs)	30%
Large cohort studies					
Senthi 2012[36]	676	33	89% (5 yrs)	<40%/>60%** (5 yrs)	N.S
Grills 2012[35]	483	1.3 yrs	91% 3 yrs	48%/77% (3 yrs)	2% ≥ G3 pneumonitis

*FU: follow-up. LC: local control. OS: overall survival. CSS: cancer specific survival. G3: grade 3. N.S not stipulated. * Patient cohort in study II in this thesis.** As measured from the KM-graph*

Conditions for evaluating the late effects of SBRT are at this time unfavorable; patients in retrospective material may have a long follow-up[38-40] but the material is often compromised with limitations such as different dose fractionation schedules, the possibility of both under- and over reporting of toxicity and heterogeneity within the patient cohorts. Japanese studies

often have a long follow-up, but have included a high number of operable patients and use iso-center dosage[39,41] making comparison to this study's material difficult. The RTOG 0236 study, a phase II study treating medically inoperable NSCLC with SBRT, recently updated their results after a median follow-up of 4.0 years and showed high local control, minimal late presenting toxicity but, surprisingly, 20% of loco-lobar recurrence[34].

There is limited knowledge on the frequency of late local failures as well as on which types of tumors relapse locally after several years and the underlying biological mechanism. Two reports[41,42] have noted that late local relapses have evolved from small tumors which is an interesting finding, since large tumor size otherwise is considered a risk factor for local relapse. Tumor tissue samples are of utmost importance to evaluate tumor characteristics, but unfortunately, patients with NSCLC often have a significant history of smoking causing reduced pulmonary capacity, which might exclude them from invasive diagnosis (transthoracic biopsy) due to the risk of pneumothorax. In the absence of a tissue sample, the cancer diagnosis is based solely on radiological examinations. From a diagnostic point of view, even though histo-pathological verification of the lesion is important, the risk of treating a benign lung lesion is less than 5% given radiological signs of malignancy and positive ^{18}F-FDG-uptake on PET, as concluded from Dutch research [43]. From a research perspective or in the setting of a new lesion or suspicion of recurrence, however, there was a substantial lack of specific information. An equally important and sometimes complicated matter is the diagnosis of a suspected local relapse. If a local relapse is suspected and the patient is excluded from lung biopsy due to poor pulmonary function, both high-risk-CT-features[44] and PET-CT[45] are non-invasive methods with >90% sensitivity and specificity for detecting a local relapse, remain limited here as well the lack of tissue material for further analyses of tumor characteristics.

When avoiding and assessing out-of-field failures (failures outside the irradiated field) it is important to divide such occurrences into two different categories; proper staging of the disease prior to primary curative treatment and proper diagnosis of a suspected recurrence. Patterns of failure, after SBRT of early stage NSCLC, were thoroughly analyzed in a large cohort study[36]. In this analysis, regional control rate at 2 and 5 years were 92.2% and 87.3% respectively and the median time to regional recurrence was 13.1 months. From this same study, distant control rate at 2 and 5 years were 85.3% and 80.1% respectively and the median time to distant recurrence was 9.6 months. Systemic failure is probably partly explained by the under diagnosis of occult systemic disease already present at diagnosis. PET-CT discovered small metastatic lesions in lymph nodes and in other organs, thereby an improved accuracy in staging [43] which is important for deciding on proper treatment. During follow-up, suspected out-of-field failures need proper diagnostic evaluation. However, if a suspected lesion appears in the lung, there might be an uncertainty if this is a new primary lung cancer, occurring in 7-8% of the patients in follow-up in surgical material[18,46], or a relapse from the previously irradiated lung cancer.

1.3.2 SBRT in the treatment of metastases

1.3.2.1 The oligometastatic state

Patients with spread disease are generally not candidates for curative treatment and receive radiotherapy and systemic treatment with palliative intent to prolong life and reduce cancer morbidity symptoms. However here, SBRT has evolved as a treatment modality and may be used in selected cases with metastatic disease such as after mixed response to systemic therapy, metastases threatening vital organ functions and in the oligometastatic setting. In 1995 the oligometastatic state was proposed by Hellman and Weichselbaum[47], describing a state where the metastases are limited in number and location. Although often referred to as maximum five metastatic lesions, the oligometastatic state is not bound to a certain number of lesions and one might also consider that the number of organ systems affected by metastatic disease could be of major importance.

In the oligometastatic state, systemic therapy for microscopic disease in combination with aggressive local treatment of the metastases may render improved outcome with control of the cancer and longtime survivorship, a current hypothesis being investigated in ongoing prospective trials. Metastasectomy of oligometastatic colorectal cancer in the liver and lung is used regularly in the clinic and conceptually concordant, one might consider SBRT in order to completely eradicate all macroscopic tumor lesions in an oligometastatic situation. Favorable outcomes have been reported after both surgical treatment[48,49] and SBRT of oligometastatic disease[49-51]. An upcoming challenge for oncology is how to pick out the patients with true oligometastatic disease who will benefit the most from the use of SBRT to eradicate visible oligometastatic disease.

1.3.2.2 Lung and liver metastases

To better understand the side effects that could develop post SBRT there is a need to describe the basic anatomy of the organs and the definitions used in SBRT and their background. Traditionally in SBRT, a lung target is categorized as being either peripherally or centrally located. The central location has historically been set to reside within or touching a 2-cm-zone around the proximal bronchial tree (the carina, the main bronchi, the intermedius bronchus and the lobar bronchi)[4], over time occasionally adding a zone around the mediastinal structures as well. At Karolinska since 2011, this definition has been tightened up to within 1 cm of the proximal bronchial tree. The peripherally located tumors are outside the 1- or 2-cm-zone and the centrally located lesions are within the zone or touching it from outside. Centrally located tumors are likely to be in the vicinity of radiation sensitive OAR such as the bronchi, the esophagus and the heart, from which severe side effects may possibly develop.

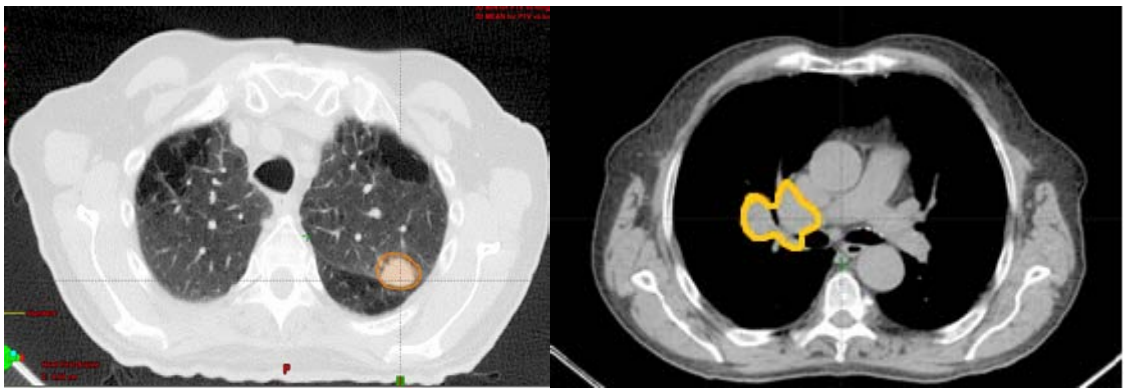


Figure 2: The two dose planning pictures show a typical peripherally located tumor (left) and a typically centrally located tumor (right).

From a side effect point of view, both the liver and the peripheral parts of the lungs are tissues with "parallel organization" which mean that they are constructed by functional subunits (FSU) (ex alveoli/capillary in the peripheral lung) that work independently to perform their function. This is to be compared to a serially functioning tissue (ex spinal cord) where the FSU work together to perform their task. Radiotherapy induced toxic effects in parallel functioning organs are typically related to the irradiated volume of the organ whereas serially functioning tissue is more susceptible to high maximum doses, sometimes to a minimal volume. Radiation induced harm to the periphery of the lung will leave the rest of the lung intact and functional whereas a too high dose to the spinal cord will cause loss of all function distal to the injury. From this thesis, toxicity to parallel functional tissue is addressed above all for lung (study I, II, IV) and toxicity to serially functional tissue is addressed specifically for the plexus and to some extent the gastrointestinal tract (study III, IV).

Metastatic disease in the lung and liver is common and these organs constitute the two organs most often treated with SBRT. Primary tumors that often metastasize to the lung include lung -, colorectal -, renal-, breast cancer and sarcoma and correspondingly, liver metastases are common in colorectal -, breast- and lung cancer as well as in other primaries. SBRT has been used successfully in treating lung metastases from a variety of primary tumors[52] including traditionally radiotherapy resistant tumors with low α/β-values such as renal cell carcinoma [53] and sarcoma [54]. With the exception of colorectal cancer metastases, which traditionally are treated with even higher doses (17Gyx3 prescribed to about the 67% isodose line at Karolinska for colorectal metastases), all tumors are treated with the same fractionation schedule regardless of primary origin and histology. Liver metastases have also been successfully treated with local control rates of >90% at one and two years respectively and with limited toxicity[55,56].

1.3.2.3 Adrenal metastases

Adrenal gland metastases are being specifically addressed in this thesis in paper III and to understand the consequences of SBRT and how to interpret the results in paper III, the basic

anatomy and physiology of the adrenals as well as the diagnostic work up for adrenal metastases are described.

The adrenal glands are paired organs, situated anterio-superior and slightly medial to the upper part of the kidney. They are enclosed by a fibrous capsule and a cushion of fat that lie on top of each kidney, encapsulated by perirenal fascia from which they are connected to the diaphragm. The adrenal glands have rich blood supply from the superior, middle and inferior suprarenal arteries, which derive from the inferior phrenic artery, the abdominal aorta and from the renal artery respectively. They drain in the suprarenal vein and the lymphatic drainage pass to the lumbar lymph nodes[57]. The rich blood supply then renders them susceptible to metastatic disease, especially breast cancer [58], lung cancer [58,59] and cancer from the stomach [58,59].

Adrenal masses discovered accidently at routine radiologic examinations – incidentalomas – are also common with an incidence of approximately 5% in the population going through imaging, 2-3% of those being malignant[60]. However, in a cohort of patients with ongoing cancer an accidently discovered lesion is malignant in~50% of the cases[61] which demands for accurate diagnosis and in a patient with a known neoplasm, an adrenal mass should always be suspected for metastasis unless definitive diagnosis of a benign lesion is possible[62]. The radiological diagnostic work-up of suspected adrenal metastases, often initiate with controlling the size of the lesion and whether it has grown over time (likely for malignancy). Second, a non-enhanced CT followed by washout studies is performed where attenuation values >10 HU and delayed washout suggest malignancy. Further investigations include MRI, showing low T1- and increased T2-signal with progressive enhancement for malignancy, and PET-CT, showing high SUV-value for malignancy[60,62]. Image-guided adrenal biopsy is an invasive method yet has a diagnostic accuracy of 96% and has a low probability of complications[63].

Adrenal metastases are often clinically silent, only about 4% of the patients present symptoms[59], such as pain, adrenal insufficiency and peritoneal hemorrhage being most frequent. CFRT with doses of 1.7-3.0 Gy per fraction up till total doses of 29-45Gy, reduce pain symptoms with an approximately 75% response rate[64].

The treatment of adrenal metastases is based on the extent of tumor burden and the patient´s general condition. The local treatment of choice is surgery which has 1-year local control rates of 77-93% dependent on tumor size [65], when bearing in mind the potential selection bias of healthier patients with favorable tumor biology in surgical materials. Complication rates depend on surgical technique and ranges between 4-34% for all complications and 0-11% for major complications [65]. If technically possible, surgery can be performed with laparoscopic technique [66], reducing the operative time, the lengths of hospital stay, the estimated blood loss and the overall complications [65].

SBRT of adrenal metastases have shown a wide range of local control between 55-100% [67-76] and mild side effects, only two reports specifically addressing adrenal metastases describe

grade 3 events (nausea, hematologic toxicity[76]) and gastric ulcer (grade 2) [72]. Four reports describe local control of 82-100%[67,68,71,76] being comparable to other SBRT treatment sites and to surgery. However, the investigated patient cohorts are small and the follow-up is limited to less than 1.5 years (Table III), potentially hiding local recurrences and limiting the interpretation possibilities.

Table III Analyses of SBRT-adrenals showing high local control rates

Study	No of pts	SBRT	Median-FU	LC	Time to LF
	n	*Gy/fractions*	*m*	*rate*	*m*
Cassamassima 2012[68]	48	36/#3*	16.2	90% (2 yrs)	4.9
Ahmed 2013[67]	13	33.75-60/#5	OS 7.2	100%	-
Katoh 2008[71]	9	48Gy/#8**	16	100% (1 yr)	-
Li 2013[76]	26	30-50Gy/#3-5	OS 17	82%/100%§	N.S

*FU: follow-up. LC: local control. LF: local failure. N.S: not stipulated. OS: overall survival. *prescribed dose to the majority of the patients. **prescribed to all but one patient.§82% for patients with prescribed doses <100Gy (BED_{10}) and 100% for patients with prescribed doses≥100Gy (BED_{10}).*

Given the success of local treatment of adrenal metastases, the question in this situation remains: which patients should be treated. Single adrenal metastasis from NSCLC is a special entity, and treatment with surgery for these patients has reported beneficial outcome with 5-year-overall survival rates of 25%-34% [77,78], favoring adrenal gland metastases ipsilateral to the primary tumor and node negative disease[78]. The underlying mechanism may be a lymphatic spread through direct lymphatic communication between the lung and the abdomen[79], mimicking a regional extension of the disease. One criticism of this theory is that a single metastatic spread may also reflect less aggressive tumor biology, regardless of treatment of the metastasis[80]. SBRT with curative intent for isolated adrenal metastasis from NSCLC has been reported in only two analyses[70,72] and although the patient cohorts are small with 8-13 patients, the outcome is favorable among long-term survivors[72] and median progression free survival of 12 months[70], respectively. Another report comparing SBRT and adrenalectomy for patients with different primary tumors and single adrenal metastases showed comparable overall survival rates at one year of 62% and 77% respectively ($p>0.05$), suggestive for SBRT to be a non-invasive alternative to surgery for isolated adrenal metastases[81].

1.4 TOXIC EFFECTS OF SBRT

The clinical success of SBRT has brought about a desire from clinicians to treat targets in radiotherapy-technically complicated situations with SBRT and to combine ablative radiotherapy with systemic treatment, not just aiming for local control, but also to increase survival rates even in metastatic patients. Although SBRT has few and mildly reported side effects, there is limited data on tolerance levels of radiation for OAR using these high fraction doses. Many of the commonly used dose constraints as well as the concept of risk-adapted therapy are direct extrapolations from CFRT and one remains uncertain, if such assumptions and constraints are valid for high-fraction-regimens. Thoroughly addressing toxicity from SBRT-treatments and correlate the presented symptoms to dose-volumetric and clinical data is of crucial importance to further develop the clinical implications of the technique.

Generally, the clinical impression of treatment related toxicity of SBRT of peripherally located lung lesions, is that the most common side effects are mild and transient and consist of skin rash, fibrosis in the high-dose area and a related cough. The Nordic phase II trial of SBRT treated NSCLC reported grade 1-2 pneumonitis 18% [5] grade 1-2 dyspnea 18% [5] and grade 1-2 fibrosis 35% [5]. Serious toxicity (grade 3-4) in prospective trials have been reported in the range of 16-30% [5,6,32] and mainly consisted of pulmonary related symptoms, with the majority presenting within the first year post treatment[5]. A higher rate of serious toxicity has been noted with centrally located lesions and the apical part of the lung is another area that needs to be approached with caution, when taking into consideration the brachial plexus which may be at risk for highly absorbed doses.

1.4.1 Pneumonitis and fibrosis

Symptomatic **pneumonitis** is a clinical condition marked by dyspnea, cough, fever and thoracic pain. To assess risk of radiation pneumonitis a commonly used dosimetric parameter is V_{20}[82], which describes the percentage of the lung volume receiving 20Gy or more. In the everyday clinic during radiochemotherapy with CFRT for locally advanced NSCLC, V_{20} is to be kept <35% to reduce the risk of pneumonitis. After CFRT, the symptoms usually start within the first few weeks after radiotherapy completion. The pathophysiology of the condition is believed to be caused by an inflammation in the alveoli of the lung and the histological findings of the acute phase comprise edema in the alveolar septae and hyperplasia of the alveolar lining cells as well as in increase of alveolar macrophages and fibroblasts [83]. The incidence of symptomatic radiation pneumonitis post SBRT range from 9-20%, presenting after a median time of 3-5 months[84-87], but may appear as late as 16 months post treatment[85]. The radiological signs of severe pneumonitis as presented earlier when compared to mild pneumonitis[88]. There is an inconsistency in the reports on risk factors, different analyses reporting dose-volumetric risk factor such as MLD[89 84,86,87], V5[89], V10 [89,90], V20 [86,87], V25 [85], and PTV [85,91]. However, in a large analysis of 483 patients (7% experiencing ≥ grade 2 pneumonitis), no dose-volume related risk factors were significant predictors for pneumonitis ≥grade 2[35] and similarly, in an analysis of 236 patients, 12% developing symptomatic pneumonitis, no dosimetric factor was predictive in multivariate

analysis although clinical risk factors of female gender, pack-years of smoking and larger IGTV and PTV were [91]. Considering these large discrepancies between these analyses, there were no certain dose-volume parameters that could be used for predicting the incidence of lung toxicity. Thus the contention here would be the individually important elements with regard to pneumonitis.

Another aspect of radiation induced lung injury is whether patients with decreased pulmonary function are at greater risk for pneumonitis when compared to patients with normal lung function. The first report on the patient material in study II did not show an increased risk for radiation pneumonitis for patients with severe COPD versus patients with cardiovascular disease[5]. Patients with severe COPD might even have a reduced risk for radiation pneumonitis as compared to patients with milder COPD [92], possibly explained by the "tissue amount" theory, claiming that patients with severe COPD have less lung tissue to generate an inflammatory response and thus have a lower risk of pneumonitis. There is further support here that there is a known increased risk for radiation pneumonitis in patients with radiological signs of interstitial lung disease [93] as well as from an analysis comprising the highest rate of pneumonitis included approximately 30% operable patients [85].

Radiation induced fibrosis is a dose/volume related condition characterized by fibrotic changes in the high dose region, radiologically presented as dense consolidation and retraction of pulmonary tissue [94] (Fig 3). Fibrosis is a dynamic process starting at 6-12 months post treatment with remodeling that continues on for several years[94]. The radiological characteristics are seen in up to 100% of the patients [95], only a few cases being symptomatic though[6,38,95].

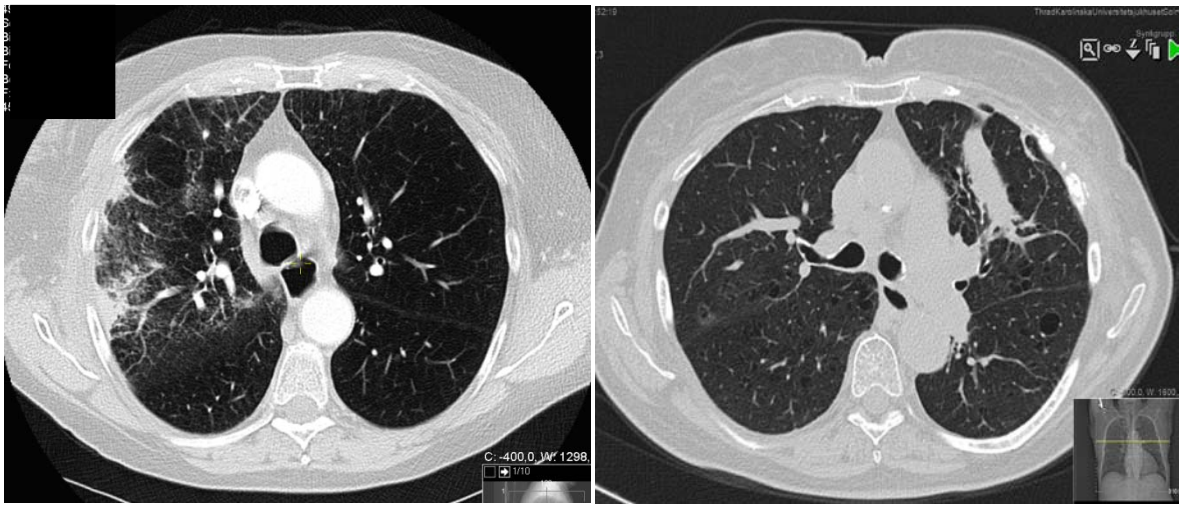


Figure 3: Pneumonitis approximately 5 months post SBRT (left picture) and fibrosis (right picture).

1.4.2 Chest wall toxicity and rib fractures

Treating lung tumors located adherent to or close to the rib cage may result in highly absorbed doses to the chest wall and to the ribs, causing chest wall toxicity with thoracic pain and rib fractures. From its earliest onset, thoracic pain is often transient and can be treated with corticosteroids, whereas any suffering recurring pain responded poorly to pain medication. Improvement of pain symptoms may be seen after a median of 4-6 months [96,97]. Prospective trials and the growth in clinical experience have drawn attention to these morbidity symptoms and both thoracic pain and rib fractures have then been addressed in specific analyses, aiming at evaluating the clinical development as well as both the dose-volumetric and clinical risk factors. Chest wall pain, often developing at a median of 7-9 months post treatment [96-98], occur in a frequency of 11-42% (all grades) [96-100] and 13-32% (≥grade 2)[96-98] either isolated or in combination with rib fractures. Rib fractures, generally appear later after approximately 2 years [97,99] and are somewhat less common, reported frequencies ranging between 1.6-23%[96,97,99-101], the highest numbers representing both symptomatic and non-symptomatic fractures [101]. Interestingly, radiological findings of chest wall edema, thinning of the cortex and osteosclerosis have been correlated with, and tending to precede rib fractures [102]. Clinical and tumor related risk factors for chest wall pain and/or rib fractures include female gender [101,103], small tumor-chest wall distance [99,101], large PTV [98,99], high BMI[100,104] especially for diabetics [100] and both young age [99] and old age have been reported, the latter for radiation induced bone injury [103].

Dose tolerance limits for the chest wall are currently not well known. Based on the performed analyses comprehensive dose constraints are hard to establish due to the heterogeneity in the patient materials with different fractionation schedules, the different delineation techniques of the chest wall and the different clinical findings. However, for a 3-5 fraction treatment V_{30Gy} [96-98,100] seems important and may be restricted to 30cc [96] or 70 cc [97], although in addition to dosimetric variables, clinical characteristics are also a required consideration [100,103]. Risk adapted fractionation schedules with five or ten fractions have also been suggested, with low reported toxicity of chest wall pain $\leq$12% and rib fractures <2%[99,105]. Currently at Karolinska, tumors are treated in the vicinity of the chest wall with 3-8 fractions, limiting the dose to the chest wall for a three-fraction-treatment to V_{30Gy}<70 cc.

1.4.3 General pulmonary toxicity

The interpretation, especially in retrospective material, of side effects of general character such as **dyspnea, cough, fatigue, COPD-exacerbation and pneumonia,** is influenced by considerable uncertainties as to whether the symptom is attributed to the treatment or the intercurrent disease. Patients with medically inoperable NSCLC, often due to COPD or cardiovascular disease (CVD), diagnosis has shown already to suffer from respiratory symptoms. Dyspnea, cough and COPD-exacerbations are parts of the picture of COPD. In prospective trials these symptoms have occurred in a clinically acceptable frequency and

grade and dose-volumetric parameters have not been coupled to the aggravation of dyspnea post treatment[106].

When assessing a patient for risk of developing radiation induced side effects, traditionally Normal Tissue Complication Probability Models (NTCP-models) estimating the risk of developing a side effect in relation to dose to the OAR, have been used. The NTCP-models are based on dosimetric data from the dose-volume histograms and on toxicity. The probability of developing the side effect may then be estimated from the model (The creation of a NTCP-model is described in section 2.4 Analyses, Material and Methods). The traditional NTCP-models, however, do not consider **patient related factors**, such as performance status, lung function, smoking status, other treatments, the patient's general condition and the individual radio-sensitivity, which might be of major importance. Mathematical modeling, using machine learning systems on large data sets, where both patient characteristics and dose-volumetric features are included, which are being developed in order to help foresee toxicity like dyspnea[107].

1.4.4 Pulmonary function changes

An interesting aspect of radiation-induced toxicity is the possible decline in pulmonary function capacity over time as measured by pulmonary function tests (PFT). The most commonly evaluated parameters in this setting are FEV1, FEV1% and DLCO. From the first report on the material presented in study II presented in this thesis, no decline in FEV1% could be established for the cohort at a median time of 14 months post SBRT [5].

Results from pulmonary function tests post SBRT are diverse, with reports of small, yet statistically significant decreases in PFTs over time [108,109] and DLCO [110] respectively, as well as reports showing no statistically confirmed changes [111-114], two of them being long-term follow-up with 3-year-data, unfortunately based on only having very few patients [111,112]. A dose-effect relationship for pulmonary function changes has not been proven[109]. Notably, when interpreting these results, progressive decline in lung function over time can be expected for patients affected by COPD, causing interpretation difficulties as to whether the decline is treatment related or caused by the underlying COPD.

A very important aspect is, given a low pretreatment pulmonary function, an elevated risk for pulmonary toxicity [108,110,113] or inferior overall survival [110,113,114] could not be confirmed in the majority of analyses and therefore poor pulmonary function alone should not exclude patients from SBRT.

1.4.5 Cardiac and large vessel toxicity

Radiation therapy may damage the heart in many ways, causing pericardial and myocardial disease as well as valvular damage and injuries to the conduction system[115]. Cardiac toxicity post SBRT is reported in low incidences, primarily in the form of heart failure grade 1-3,

cardiovascular disease grade 1-2, arrhythmia grade 1-2 and non-symptomatic pericardial effusion [6,17,116,117]. Certainly, there is a substantial possibility of underreporting of cardiac side effects, partly due to the high incidence of both arrhythmias and cardiovascular disease in general, partly due to a possible misinterpretation of symptoms such as dyspnea as a result of subclinical heart failure. In assessing dose to the heart, we normally delineate the heart as one homogenous mass and do not consider which functionally different parts of the heart are at greatest risk for radiation induced injury and what dose-volume parameter that part of the heart might be more sensitive to.

The large vessels in the mediastinum are another OAR, which might be at risk during radiation therapy; dependent upon the target location. Little is known on their tolerance from SBRT-regimens, and currently at Karolinska we do not use any restrictions for the great vessels in the mediastinum. Of interest here, a recent report from Japan on centrally located tumors, compared their clinical outcome of toxicity to the dose constraints defined by the University of Texas Medical Center[118], and based on the recorded toxicity, suggested that the aorta, v cava and pulmonary vein may show a greater tolerance to radiotherapy as compared to the pulmonary artery and the bronchus, particularly in the pulmonary hilus[119]. It remains hopeful that this encouraging aspect will be further heightened with the results from the RTOG 0813 and the ongoing HILUS-trial, being conducted by the Nordic SBRT-study group.

1.4.6 Central airways toxicity

Ever since the first report of increased toxicity after SBRT of centrally located lung lesions[4], uncertainty prevails on just how to treat these lesions with radiotherapy. In a prospectively collected cohort of 70 patients, 22 being centrally located and treated with 60-66Gy in three fractions depending on tumor size, Timmerman et al reported increasing risk for grade 3-5 toxicity for centrally located tumors [4]. The results were updated in 2009 after a median follow-up of 50 months, describing grade 3-5 side effects in the form of apnea (n=1), pleura effusion (n=2), decline in pulmonary function tests values (n=2), pneumonia (n=4), hemoptysis (n=1) and respiratory failure (n=1). These last three symptoms being deadly for five patients[32]. Also, serious toxicity in form of tracheal necrosis, esophageal ulcers and bronchial strictures has also been described in the literature.

More recent reports have described acceptable toxicity [116,120-124] and local control rates of ≥85%, given a BED_{10} of ≥100Gy for centrally located lesions [116,123,124]. The largest report constitutes a systematic review of 563 lung tumors from 20 different analyses from which the authors have concluded that when utilizing appropriate fractionation schedules with BED_{10} ≥100Gy and BED_3≤210Gy, treatment related mortality was <1% and local control ≥85%. From the same report, grade 3-4 toxicity was <9% [123]. Thus, there is a growing body of evidence for safely treating centrally located tumors with SBRT; however data on dose constraints for organs at risk remain scarce. Currently, the results from the RTOG 0813-trial, a prospective dose escalation phase I/II trial, are pending and patient accrual for the HILUS-trial, a phase II-trial evaluating local control and toxicity for 7Gyx8 for tumors within 1 cm

from the proximal bronchial tree, conducted within the Nordic countries, is almost finalized. Data from these prospective trials will be of key importance in the further evaluation of SBRT of centrally located lesions.

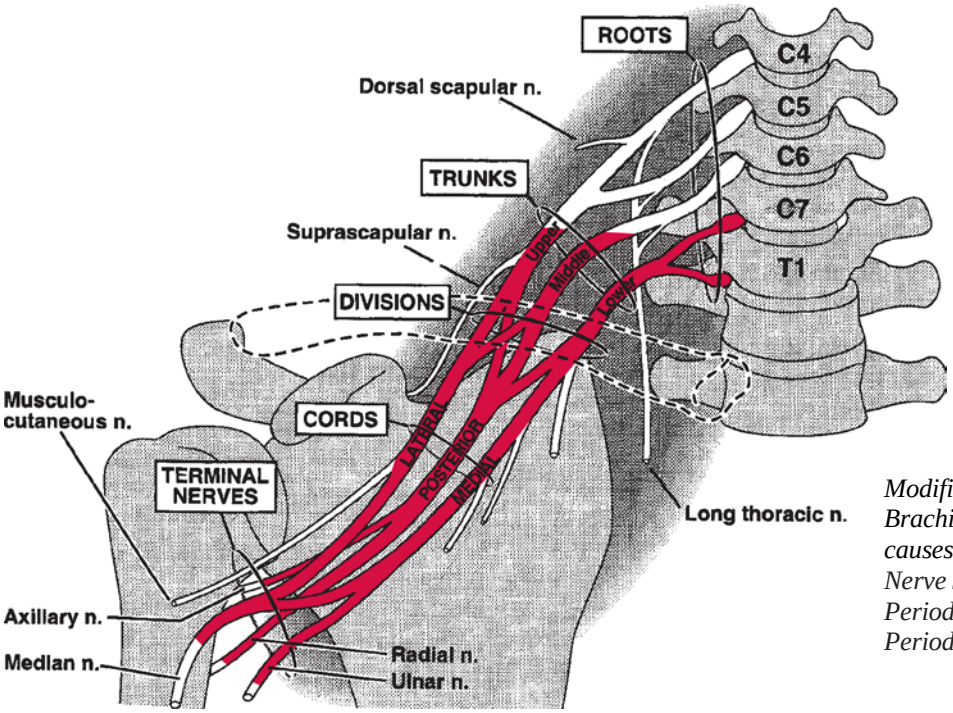
The tolerance levels for high-fraction doses of the central airway structures are not very well known. Currently at Karolinska, patients with centrally located lesions (within 1 cm from the proximal bronchial tree) are treated with 7Gyx8 with dose guidelines of maximum 7Gyx8 ($BED_{3,max}$ 187Gy) to the ipsilateral bronchus and hard dose constraints of 6.1Gyx8 ($BED_{3,max}$ 148Gy) to the contralateral main bronchus and trachea. These constraints are based on a retrospective analysis from the Nordic SBRT group evaluating bronchial toxicity post SBRT with radiation induced atelectasis as surrogate for bronchial toxicity. No atelectasis was noted below the corresponding dose of 6.5Gyx8 (BED_3 =165Gy)[125]. Except for dose restrictions that can be withdrawn from the DVHs, in the everyday clinic we try to avoid irradiating the entire circumference of a main bronchus and not to irradiate any lesion reaching through the wall of a main bronchus visible on a CT-scan.

Another noteworthy characteristic is the possible mechanism and increased risk of toxicity for centrally located lesions. The most common type of grade 3-4 toxicity is pneumonitis, pneumonia, dyspnea and bronchial strictures whereas the most common toxic deaths have been attributed to direct bronchial injury (stenosis/strictures/fistula) and hemoptysis [123]. A possible explanation for pneumonitis and pneumonia might be that the central airways, as opposed to the lung parenchyma, are not sterile. One could further hypothesize that a radiation induced minor injury in this situation may be complicated with reduced ventilation and bacterial colonization and thus have a reduced chance to heal itself. The bronchi are also considered a serially functioning organ where an injury will lead to the disruption of the function of the organ distant to the injury. Direct bronchial injury and hemoptysis may reflect a serious radiation induced wound; whether healing with a fibrous scar or not healing.

1.4.7 Radiation induced brachial plexopathy

1.4.7.1 Brachial plexus

The brachial plexus is one of the main OAR when treating apically located lung lesions and it is important to understand the **anatomic definition and the function** of the plexus to foresee the physical impairment that a lesion causes. The brachial plexus is a complicated structure extending from the spinal cord to the axilla. It is formed by the roots exiting C5-T1 (fig 4), which form three trunks that pass behind the clavicle and the sternocleidomastoid. The lower trunk lies in close proximity to the apex of the lung, being at risk during SBRT-treatment of apical lung lesions. Retroclavicularly, the trunks divide into anterior and posterior divisions, which form three cords, defined as the posterior, the lateral and the medial, with respect to their relation to the axillary artery. The medial cord is an extension of the anterior division of the lower trunk and gives rise to the ulnar nerve and the medial head of the median nerve. The lateral cord is formed by divisions from the upper and middle trunks and the posterior cord is formed by the posterior divisions from all trunks[126] .



*Modified illustration: Ferrante M; Brachial plexopathies: classification, causes, and consequences[123]; Muscle Nerve **30:** 547–568, 2004, Wiley Periodicals, Inc.© 2004 Wiley Periodicals, Inc. (By permission)*

Figure 4: Anatomical description of the brachial plexus. The red marking in the picture describes the part of the plexus delineated in study IV.

As shown above, the plexus is a complicated structure with a complicated **physiology** where the extent of functional impairment following an injury to the structure, will depend on the location on the lesion. In SBRT of apically situated lung lesions, the greatest risk for plexus injury prevails in the parts running close to the lung structure i. e the lower trunk and the cords[126].

1.4.7.2 Radiation induced brachial plexopathy

Radiation induced brachial plexopathy (RIBP) is a condition characterized by numbness, pain, paresthesia and motor deficit in the affected upper extremity. The occurrence of RIBP has been reported since the 1960s, mainly in breast cancer treatments. Clinically, the symptoms of RIBP after CFRT often present with paresthesia [127-131] (and swelling and heaviness of the arm[129]) later developing into a picture reflecting a complex neural injury with symptoms of paresthesia /numbness, pain and motor weakness[127,128,132,133]. The latency period from radiation therapy to the first symptom ranges from immediate onset till 26 years post treatment[129-135], three series reported a median time of ≥ 1 year post treatment[127,129,131]. Of interest though, one report has suggested that the initial symptoms may appear earlier with higher doses[131], a finding which is in line with results from our analysis (Study No. IV in this thesis); where all the cases had presented symptoms within 13 months.

The **clinical development** of RIBP is in most cases considered progressive and the symptoms irreversible, however reports on spontaneous improvement do exist [131,136,137]. Objective signs of RIBP on clinical examinations include decreased/absent muscle stretch reflexes,

hypestesia/hypalgesia and weakness[130,133]. Neurophysiological examinations typically reveal demyelinating conduction block on motor nerve conduction studies and myokymic discharge and fasciculation potentials on needle examination evaluations[126,128,133,138]. A clinically important finding is that patients showing clinical symptoms and signs of RIBP also present significant abnormalities on neurophysiologic examinations[133], showing that clinical findings are concordant with objective neurophysiological findings.

The theory of the underlying **mechanism behind RIBP** constitutes of an initial microvascular injury and later on radiation induced fibrosis and a direct neurological injury[137]. Radiation induced fibrosis itself is a progressive state, going from chronic asymptomatic inflammation to a poorly vascularized phase with retractile fibrosis[139]. From autopsy material, one case with RIBP was recorded with signs of extensive fibrosis whereas two patients with fewer or no symptoms had not shown or did show only minimal fibrosis[131]. The long latency period of RIBP may be explained by the "double crush" phenomenon[140] which, although debated[141], suggests that a nerve suffering a first minor trauma is more susceptible to a second injury or compression.

1.4.7.3 Dose constraints to the brachial plexus

Another question is how sensitive the brachial plexus is to radiation therapy and what dose guidelines to the brachial plexus should be recommended. Risk factors for RIBP include high fraction doses, high total doses, chemotherapy, high or young age just to mention a few[137]. In CFRT there are several reports on RIBP and Emami-data that suggest neurological injury, TD5/5 (the probability of 5% complication within 5 years from treatment) of the plexus does occur at about 60-62Gy in 1.8-2-Gy fractions[142] and current trials for head-and-neck cancer conducted within the RTOG had used dose-constraints in the order of 60-66 Gy[143]. However, there have been appeals to increase the dose to the tumor to achieve tumor control that do prescribe an increase allowable dose to the plexus area. Eblan and colleagues[132] have proposed to push the dose constraints (CFRT for radiochemotherapy for lung cancer) to D_{max} $\leq$78Gy (BED_3 130Gy) and V_{76Gy} $\leq$1cc (BED_3 127Gy), with their motivation that the risk of RIBP must be weighted against the risk of a sublethal dose to the tumor, leading to local failure with tumor growth into the plexus and extensive morbidity symptoms[132]. In SBRT research, there are just three reports specifically addressing this issue[116,136,144]. A summary of the results is shown in table IV.

Table IV Summary of studies addressing RIPB post SBRT

Study	Tumors		Dose to the plexus		RIBP	Conclusion – new plexus dose restriction
		n	$BED_{3,max}$	V_{30Gy}*	*Grade & no of pts*	
Forquer 2009[136]	RIBP-	30	84Gy (10-851)	-	-	D_{max} <26 Gy for 3 or 4 fractions
	RIBP+	7	123Gy (45-839)	-	G2:4; G3:2; G4:1	
Chang 2014[116]	RIBP -	7**	≤137Gy	≤0.2 cc	-	D_{max} ≤35 Gy and V_{30Gy}≤0.2cc for 4 fractions
	RIBP+	3	>137Gy	>0.2 cc	G2-3: 3	

*Doses described to the patients with and without RIBP in two studies addressing RIBP specifically. RIBP+: radiation induced brachial plexopathy. RIBP-: no radiation induced brachial plexopathy. $BED_{3,max}$: maximum dose to the plexus in BED_3. V_{30Gy}:volume of the plexus receiving ≥30Gy.*Four-fraction-treatment.**Three additional patients, treated with 10Gyx7 were at risk for RIBP, but did not develop RIBP and doses to the brachial plexus were not stipulated.*

1.4.8 Stomach and intestinal toxicity

Treating target lesions in the abdomen with SBRT could be a delicate matter when delivering ablative doses; maintenance of a balance in order to achieve local control while at the same time avoiding an over-dosage of the OAR, a possible occurrence in the stomach or intestines. An injury to the GI-tract may be present as general symptoms of nausea, vomiting or abdominal pain or it may reflect a direct localized injury and present itself as an ulceration, a perforation, a stenosis or a bleeding from the injured spot. When treating abdominal targets, the parts of the GI-tract frequently at risk are the stomach (treatment of left sided adrenal metastases and lymph nodes), the duodenum (treatment of right sided adrenal metastases, pancreatic carcinoma especially in the head of the pancreas, liver targets) and the small bowel (treatment of adrenal metastases, lymph nodes, pancreatic carcinoma etc).

Whereas lung toxicity post SBRT of peripherally located lesions often is endurable for the patient, gastrointestinal toxicity can be life threatening and require surgical intervention. Nausea and vomiting as well as pain are frequently reported side effects after SBRT of abdominal targets, the former occurring in a frequency of approximately 38-40% (all grades) and the latter in a frequency of 6-30% (≥grade 2)[145,146] within 3 [145] or 6 months [146]. Gastrointestinal grade 3 and 4 toxicity presented as ulcers, nausea, diarrhea, perforations, bleeding and stenosis within one-year post treatment were the conclusion from three analyses[146-148].

Dose constraints to the GI-tract are currently quite unknown concerning high-fraction doses. At Karolinska, dose constraints with SBRT are set to EQD_2 52Gy to 5 cc (corresponding to 23.7Gy for three-fractions) of the intestine or stomach, trying to avoid irradiating the entire circumference. There are no prescribed maximum dose constraints, the underlying reason being unpublished results from our own institution where large irradiated volumes have been critical in the development causing severe side effects. Two analyses from Korea have

specifically addressed the issue of the dose volume effect and the risk for gastroduodenal [147] and intestinal toxicity[148] post SBRT. In both reports V20-V35 and D_{max} were good dosimetric predictors of both gastroduodenal and intestinal severe toxicity. Surprisingly though, for gastroduodenal toxicity D_{max} was the best dosimetric predictor, whereas V_{25Gy} was the best dosimetric predictor for intestinal toxicity. In a 3-fraction-treatment, keeping D_{max}<35Gy for the stomach and duodenum and V_{25Gy}≤20cc to the intestines may reduce the probability of severe complications to the respective organs by less than 5%[147,148] which is clinically acceptable. Apart from these dosimetric considerations, the authors also point out clinical risk factors to be any history of a previous ulcer, for gastroduodenal toxicity, and the length of treatment time, for intestinal toxicity. Although the authors had presented a large number of events relative to other reports, it was noteworthy that both these analyses comprise limited patient material which was retrospectively chosen and had excluded nausea as a toxic symptom, leading to a possibility of underreporting severe side effects. In comparison, the QUANTEC-report from 2010 suggests somewhat more careful dose constraints; to the stomach maximum 22.5Gy to approximately 5 cc or 4% and D_{max}<30Gy for a 3-fraction-treatment; and to the small bowel <30Gy for 3-5 fractions[149].

1.4.9 Adrenal insufficiency

1.4.9.1 Adrenal gland

The adrenal glands are composed of cortex (derived from the mesoderm) and medulla (derived from neural crest cells) with completely different biological functioning. The cortex is composed of two layers; the outer layer (zona glomerulosa) producing aldosterone which mainly is regulated by the renin-angiotensine-system and the inner layer (zona fasciculata/retiucluaris) producing glucucorticosteroids, androgens and small amounts of estrogens and is regulated by the adrenocorticotropic hormone system (ACTH-system)[150]. The adrenal medulla produces epinephrine (80%) and nor-epinephrine and is regulated by the sympatic nervous system[151]. Unlike the cortex, the proper functioning of the medulla is not essential to life.

1.4.9.2 Adrenal insufficiency

Adrenal insufficiency may then develop when >90% of the adrenal cortex is lost[66,150], making adrenal insufficiency to be a potentially expected side effect post SBRT. Clinical symptoms of adrenal insufficiency are characterized by fatigue, loss of appetite, weight loss, nausea, vomiting, abdominal pain, hypotension and hyperpigmentation[152]. Diagnosis is made from an ACTH-stimulation test in which S-cortisol was measured at baseline and at 30min or 60 min after parenteral administration of adrenocorticotropic hormone[152]. To separate primary (non-functioning adrenal gland) and secondary adrenal insufficiency (disturbance of the hypothalamus-pituitary gland axis), ACTH- and renin-levels in the blood may be measured; which show increased levels of primary adrenal insufficiency[152]. Treatment consists of substitution of glucocorticoids and a mineral corticoid (with primary adrenal insufficiency)[150].

Current knowledge on the radio-sensitivity of the adrenal glands remains limited. Clinically, two reports have described two cases of adrenal insufficiency grade 2 post SBRT [68,73], one presented at 2.5 years after treatment[73]. In addition two case reports described radiation induced adrenal insufficiency, one after SBRT of bilateral adrenal lesions[153] and the other one developing adrenal insufficiency after radiotherapy of the spine[154]. Notably, another case report described preserved adrenal function after 40Gy in 5 fractions to the adrenal gland despite the absence of a contralateral adrenal gland[155] that would suggest a high radio-resistance of the organ.

2 MATERIAL AND METHODS

2.1 OVERVIEW OF THE STUDIES

Table V Overview of the studies – methodology

	Study I: **Reirradiation**	*Study II:* **Long-term FU**	*Study III:* **Adrenal metastases**	*Study IV:* **Plexus toxicity**
Study character				
Type of study	Retrospective	Prospective	Retrospective	Retrospective
Treatment time period	1994-2004	2003-2005	1999-2013	2008-2013
Inclusion criteria	Reirradiation with SBRT of a previously SBRT-treated lung target. PTV:s overlapping of >50%	Peripherally located NSCLC stage I in a medically inop. patient OR refusing surgery	SBRT-treatment of an adrenal metastasis	SBRT-treatment of a lung target located superiorly to the aortic arch
Exclusion criteria	Lack of follow-up	Central location	Lack of follow-up Lack of SBRT-data	Lack of follow-up
Outcome and evaluations				
Outcome	1. Toxicity 2. Local control	1. Local control 2. Toxicity 3. Survival	1. Toxicity 2. Local control	1. RIBP 2. Toxicity
Tumor response	From records	WHO	RECIST v1.1	N.A
Toxicity scoring	CTCAE v3.0	CTCAE v4.0 RTOG (fibrosis)	CTCAE v4.0	CTCAE v4.0
Treatment characteristics				
SBRT: n(dxf) n=no of pts d= dose/fract. F=no of fract.	1 (20Gyx1) 8 (15Gyx3) 23 (15Gyx2) 1 (11Gyx3) 12 (10Gyx4) 5 (10Gyx2-3) 16 (8Gyx4-5) 1 (7Gyx3) 1 (6Gyx7)	57 (15Gyx3)	13(10Gyx3), 8(15Gyx3), 6(10Gyx4), 4(8Gyx4), 3(8Gyx5), 3(7Gyx8), 2(12Gyx4), 2(9Gyx5), 2(8Gyx3), 2(7Gyx6), 2(5Gyx5), 10Gyx5, 9Gyx3, 7Gyx3, 7Gyx2, 6.5Gyx8, 6Gyx10, 6Gyx8, 3(5Gyx12), 2(7.5Gyx8), 3Gyx15	1 (17Gyx3) 49 (15Gyx3) 1 (12Gyx4) 2 (10Gyx5) 1 (6Gyx10) 6 (7Gyx8) 1 (6.4Gyx8)
Target	Lung	Lung	Adrenal	Lung

2.2 THE RETROSPECTIVE ANALYSES

In the retrospective analyses the patients were identified from the local SBRT-list at Karolinska (study I and III) and/or the dose planning systems (study III and IV). Patients were excluded due to lack of follow-up (study I, III and IV) or if radiotherapy data was missing (study III).

Study no I and IV focus on toxicity after SBRT of lung targets. In study I, aiming to evaluate toxicity of reirradiation, all the patients reirradiated (defined as >50% overlap of the PTVs) for a lung target with SBRT after prior SBRT at Karolinska between 1994 and 2004 were included. Patients were excluded due to a lack of follow-up data. The requirement of the arbitrary definition of a 50%-overlap was based on a minimal volume of reirradiated lung. Mean lung dose (MLD) was chosen and recorded as dosimetric parameter based on the hypothesis that the lung would be the major OAR at reirradiation. Clinical toxicity was based on the patient records. Pre-specified side effects were pneumonitis, atelectasis, cough, dyspnea, obstruction/stenosis of airway, esophagitis, bleeding, pleura effusion, pulmonary fibrosis, fracture, dermatitis, hyperpigmentation, induration of the subcutis, pain and liver dysfunction. Local control was evaluated from the previously performed radiologic evaluations and largely based on the radiological statements. The Study IV aims were to evaluate RIBP post SBRT. The patients for this analysis were identified from the dose planning system and included in the analysis if they had received SBRT to a superiorly located lung target defined by the epicenter of the tumor being localized above the aortic arch. Delineation of the plexus was done retrospectively by a dedicated radiologist on the already performed non-contrast enhanced CT-scans with additional help from diagnostic imaging when needed. Toxicity was scored from the medical charts, using a modified version of the CTCAE v4.0 where pain and sensory/motor alterations in the area innervated by the brachial plexus at risk, all were considered signs of RIBP. Doses to the plexus (maximum dose, dose to 0.1cc, dose to 1cc and dose to 3 cc of the plexus at risk) were drawn from the dose volume histograms (DVH:s) and recalculated using both the linear quadratic model (LQ-model) and the Universal Survival Curve model (USC-model) and correlated to clinical symptoms of RIBP. A normal tissue complication modeling (NTCP-modeling) was fitted to the data using the maximum likelihood method. To establish a recommendable dose-constraint to the plexus, a cut-off dose foreseeing approximately a <10% risk ≥ grade 2 RIBP was appointed. The performance of the NTCP-modeling for each of the different dose

volumetric variables was tested by area under the receiver operating characteristic curve (AUC).

In study III, including patients from a wider spectrum of time (1999-2013) and from three different centers (Karolinska University Hospital, Stockholm; VU Medical Center, Amsterdam; and Rigshospitalet, Köpenhamn), the patients were identified from the local SBRT-registers or from the dose planning systems. The aim of this study was to evaluate SBRT in the treatment of adrenal gland metastases, focusing on local control and side effects. Patients treated with SBRT-technique for adrenal metastases were included. No minimum prescribed dose was required. The targets were evaluated according to RECIST v1.1 and in the majority of tumors (n=47), the local control was evaluated by a radiologist especially designated for this study. Except for a wide variety of fractionation schedules used, the treatment technique differed somewhat between the centers and over time, pointing out the use of homogenous dosage (n=3), the VMAT-treatments (n= 15) and the use of ITV (n=7). However, for all but two tumors, the CTV comprised the entire adrenal gland and a PTV-margin of 5-10 mm was added. Data on toxicity was collected from the patient records and scored according to CTCAE v4.0, pre-specified toxic symptoms were kidney injury, adrenal insufficiency, abdominal pain and diarrhea.

2.3 THE PROSPECTIVE STUDY

The basis for study II was a prospectively collected patient cohort, enrolled in a phase II trial with the primary aim to evaluate progression free survival at 36 months for medically inoperable stage I NSCLC treated with SBRT. The trial was conducted within the framework of the Nordic SBRT-study group in Denmark, Norway and Sweden, and included patients between 2003 and 2005. All the patients had peripherally located NSCLC, and were deemed medically inoperable or refused surgery. All the patients were treated with 15Gy x 3. Follow-up was regulated within the protocol within the first 36 months and after that, they were followed in accordance with clinical routines. For the long-term evaluation, clinical data was collected from the charts and radiological follow-up was assessed. Pre-specified radiological side effects included atelectasis, pneumonitis, fibrosis and pleural effusion. The main aims with the long-term follow-up were to evaluate late local relapses, late toxic effects and survival. Late presenting effects were defined as occurring >36 months.

2.4 ANALYSES OF THE MATERIAL IN THE STUDIES

2.4.1 Statistical methods in the studies

The studies in this thesis contain limited patient material (29-58 patients) having few events that do unfortunately limit the interpretation possibilities and the possibilities of statistical testing. In consultation with the statistician affiliated to this research team, statistical testing of the studies has been limited in order not to over-interpret clinical results. Generally, non-parametric tests were used for the descriptive statistics to compensate for smaller number of patient cohorts where a normal distribution could not be expected, and for potential outliers. For survival analysis (or time to event analysis), we used the Kaplan-Meier method, a non-parametric test based on the life-table technique, and often presented graphically where the curve changes when a subject fails but is stable when a subject is censored. The advantage of this method is the use of the exact time of an event for each individual in a sample and the use of time contributed from censored individuals. This method, however, was an estimation of survival function and to evaluate the uncertainty in the graph (or rate at a certain time) a 95% confidence interval could be created. This interval is based upon the standard error of the survival function, which is defined by the number of individuals at risk for the event at a certain time divided by the individuals at risk at time 0 [156]. A small patient material will generate a wider 95% confidence interval, indicating uncertainty in the analysis. In study IV we also performed a receiver operating characteristic curve analysis (ROC-analysis) to test the prognostic value of dose to the plexus in relation to outcome and the AUC was calculated.

2.4.2 NTCP-modeling in study IV

In study IV, a NTCP-model was fitted to the data for each of the dose-volume parameters (maximum dose, dose to 0.1cc, 1 cc and 3cc) to the brachial plexus. The modeling was done both for the linear quadratic model (LQ-model) using BED (α/β =3) and the single fraction equivalent dose (SFED). SFED was calculated using the USC-model (α/β=3 Gy, α=0.206 Gy^{-1}, n=10 and D_0=1.0 Gy and d_T=5.8 Gy)[157].

A cumulative normal function was used:

$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx$, where $t = \frac{\varphi - \varphi_{50}}{m \cdot \varphi_{50}}$.

ϕ50 is the dose predicting a 50% probability of normal tissue complication (in this case grade 2-3 RIBP) and *m* relates to the slope of the curve (fig 8).

The probability of developing the side effect (RIBP in this case) could be estimated. The NTCP-model was based on data withdrawn from the DVH:s, that showed doses to different

volumes of the respective risk organs. However, DVH:s did not account for the anatomical distribution of dose within the organ which might have been crucial for the development of any side effects.

2.5 EXAMPLES OF TUMOR LOCATIONS AND RISK ORGANS IN THIS THESIS

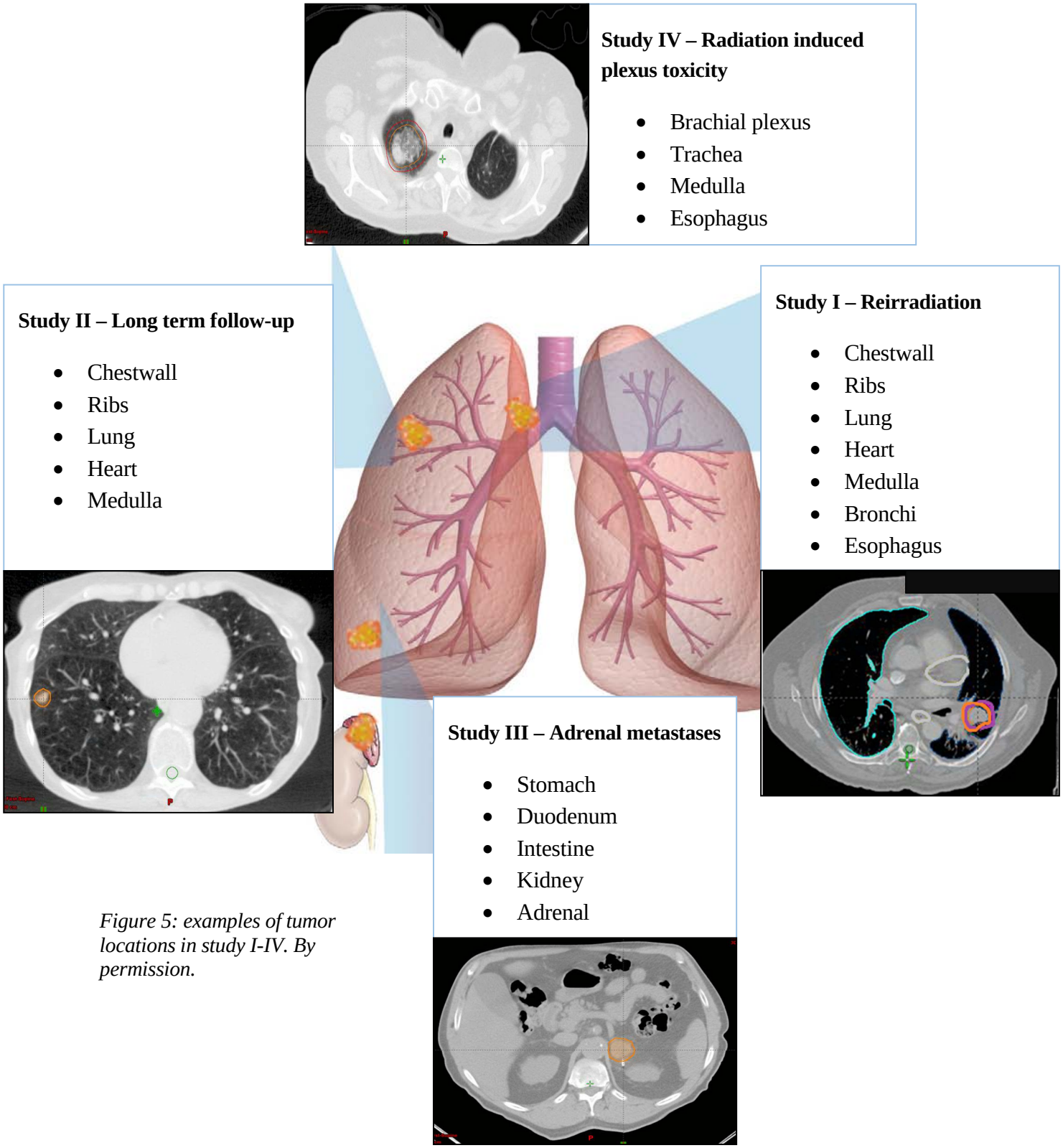


Figure 5: examples of tumor locations in study I-IV. By permission.

3 RESULTS AND DISCUSSION

3.1 OVERVIEW OF THE STUDIES

Table VI Overview of the studies – results

Study		*Study I:* **Reirradiation**	*Study II:* **Long-term FU**	*Study III:* **Adrenal metastases**	*Study IV:* **Plexus toxicity**
Cohort					
Included pts No of tumors	*n*	29 32	57 57	58 60	57 61
Excluded pts	*n*	5	3	12	0
Male/female	*%*	62/38	46/54	53/47	46/54
Median age at treatment	*yrs*	65	75	64	73
Primary NSCLC*	*%*	13%	100%	-	59%
Metastases		87%	-	100%	41%
Median follow-up time	*m*	12	41.5	12.6	24.6
Tumor control					
Local control	*%*	52% (5 m)	79% (5 yrs)	87% (2 yrs)	-
Regional control	*%*	-	82% (5 yrs)	-	-
Distant control	*%*	-	57% (5 yrs)	-	-
Toxicity					
Most common toxicity	*type*	G1-2 Cough G1-2 Atelectasis G1-2 Pulmonary fibrosis	G2-3 Dyspnea G2 Rib fracture	G1-2 Abd pain G1-2 Fatigue G1-2 Nausea	G1-2 Pneumonitis G1-2 Pain thorax
Grade 3	*type*	cough, dyspnea, pneumonitis, stenosis of airway, pain, pleural effusion, dermatitis	VT, rib fracture, dyspnea	abdominal pain, duodenal stenosis, fatigue, nausea, vomiting, loss of appetite, weight loss, pancreatitis	RIBP, musculo skeletal, pain, dyspnea, COPD-exacerb, heart failure, fever/chills.
Grade 4	*type*	V cava sup stenosis, fistula of trachea and gastric tube	-	Duodenal ulcer, gastrointestinal bleeding	Dyspnea
Grade 5	*type*	Bleeding (3 pts)	-	-	-

*Study II, late effects are presented. Study III, 60 tumors were evaluable for LC. *Curative treatment.*

3.2 TOXICITY

3.2.1 Pulmonary toxicity

3.2.1.1 General pulmonary toxicity in study I, II and IV

Pulmonary toxicity was addressed in study I, II and IV through which all had different endpoints and inclusion of different patient categories (table VI). Without focusing on the special issues addressed in the different studies, the most commonly noted toxicities were in study I cough, atelectasis and pulmonary fibrosis, in study II dyspnea and rib fracture and in study IV pneumonitis and pain in thorax. Grade 3-5 toxicity was more pronounced in study I when compared to study II and IV, which was also expected with at least one reirradiation of a previously treated target and 34% of the tumors having a central location. The different toxicity profiles may have had several reasons within the categories of patient- tumor- and treatment characteristics. A few things worth mentioning are follow-up time, tumor location (apical/central/peripheral), size of target and number of received treatments as well as patient related factors, not scored in all analyses and therefore not possible to correct for. Serious toxicity tended to develop within the first year post SBRT[6] with no increase in late toxicity after >36 months being noted in study II. However, the very limited follow-up time in study I and IV – at 12 and 24 months respectively – have led to uncertainties about whether potential side effects would have developed if the follow-up period had been longer. In addition, centrally (34% of the tumors in study I) and apically situated tumors (100% in study IV) were located closer to radiation sensitive risk organs, with patients vulnerable to side effects. Lastly, SBRT was delivered at least twice to the same part of the lung in study I, whereas multiple treatments were less frequent in study II and IV.

At Karolinska with SBRT, there were no dose constraints to the lung which differs in comparison to the recommendations in the RTOG-study protocols and to other centers[116,158]. In study I, II and IV, 11-14% of the patients developed grade 2 pneumonitis, comparable to other reports, and in study II no dose-volume risk factor for pneumonitis could be established. In fact V_{20Gy} and V_{17Gy} were even somewhat lower for patients with pneumonitis grade 2 as compared to the non-affected patients. Of interest to note here were the findings of increased risk of pneumonitis from low absorbed doses to large volumes of the lungs[89], frequently seen in VMAT treatments as compared to static field-technique, as well as the influence of dose to the heart in relation to the development of radiation pneumonitis (in CFRT)[159]. Such findings reflected on the complexity of assessing dose to risk organs in relation to the treatment technique and the clinical development of a given side effect and provide room for further elucidation. In conclusion, the basis for dose constraints to the lung in SBRT-treatment is currently scarce.

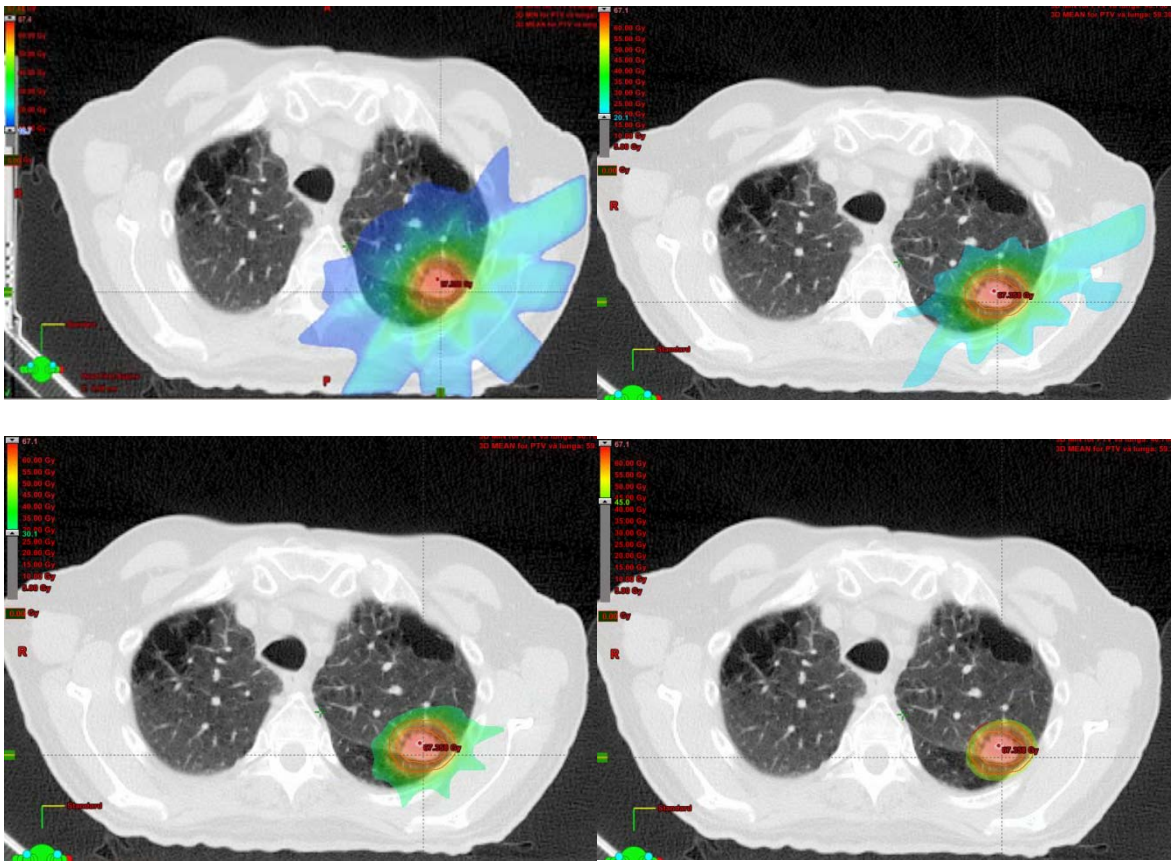


Figure 6: Dose distribution for a 3-fraction-treatment where red indicates the highest dose (67Gy), located in the tumor, and the rapid dose fall-off is then described visually by the changing colors from red-yellow-green-blue. Dose distribution for total doses A) >10Gy. B) >20y. C)>30Gy. D) >45Gy.

Addressing toxicity retrospectively, especially in patient cohorts affected by metastasized cancer and/or pulmonary disorders, are afflicted with some uncertainty. Toxic effects such as pneumonitis and fibrosis in the high dose region as well as rib fractures in close proximity to the irradiated target are most certainly treatment related whereas other symptoms may be questioned with the relationship to therapy. From this context, the retrospective methodology has a notable limitation since the recording of a side effect is dependent on information flow in several lines (patient – doctor – documentation – interpretation by researcher). However, the greatest uncertainty prevails between grades 1-2 which often are lumped together and regarded as clinically acceptable. Side effects of grade 3 and above are more likely to be stated in the chart making an underreporting less likely. The CTCAE-scale offers an objective measurement to magnify symptoms limiting the possibility of widespread grading being inaccurate. Therefore, the toxic symptoms, especially grade 3-4 in these studies were considered valid.

Except for dose to the lung as risk factor for radiation induced lung toxicity, there were also clinical risk factors, of which we know very little today. On note, in SBRT severe COPD reduces the risk of pneumonitis [92] and even patients requiring oxygen at home can be safely treated [160], whereas interstitial lung disease increases the risk [93]. One patient in study II was

inoperable due to pulmonary fibrosis and he did not develop pneumonitis, but was diagnosed with treatment induced fibrosis grade 3 at 28 months post SBRT.

In regard to risk factors for dyspnea after CFRT, current data today suggested that the impact of performance status, FEV1, smoking history and age are equally or even more important than absorbed doses to the lung from within the therapeutic dose range [107], and this model is currently being validated by a dataset of SBRT-treated patients. This becomes an interesting turn in predicting toxicity since the traditionally used NTCP-models have not taken into consideration individual clinical patient characteristics.

3.2.1.2 Toxicity of re-irradiation with SBRT after prior SBRT of lung tumors – Study I

The primary aim in study I was to evaluate toxicity after reirradiation with SBRT after prior SBRT for a lung target. Thirty-two tumors were reirradiated one time, two tumors two times and one tumor was reirradiated three times. This analysis included patients with both centrally (n=11) and peripherally (n=21) located lung tumors as defined by Timmerman[4]. Apart from the reirradiation treatment 21 patients (72%) also received additional courses of SBRT for other lung metastases, which might influence the development of toxicity. Our analysis has shown a high rate of serious toxicity with 14 recorded grade 3-4 toxic events in 8 patients and 3 toxic deaths in the form of bleeding. Noted risk factors for serious toxicity were central location, large CTV and shorter ΔT. Current data on local control and side effects of reirradiation with SBRT of a previously treated SBRT lung target remain quite limited and, apart from our analysis based on reports on 3-10 patients from small retrospective patient cohorts [161,162] or sub-analyses from larger cohorts with different types of radiation in the first and the reirradiation setting[163-166]. In the series from Hearn et al[161], 10 patients treated with SBRT of ≥100Gy (BED_{10}) in 1-5 fractions, were retreated after a median of 14.8months (9.9-26.3) with an additional course of SBRT of ≥100Gy (BED_{10}) in 3-5 fractions. In contrast to our findings, they had not recorded any grade 3-5 toxicity, possibly explained by the fact that no tumors were located within the zone of the proximal bronchial tree. Interestingly though, in spite of these high doses to the tumors, 4 tumors still relapsed after a median of 9.9 months.

The analysis of re-irradiation of this thesis comprises the largest patient cohort thus far analyzing retreatment with SBRT after prior SBRT. Grade 3-5 toxicities occurred in 11 patients (38%), which were higher as compared to other analyses of reirradiation with SBRT both after CFRT and SBRT[161,164-166]. A few analyses reported increased frequency of grade 3 toxicities[162,167-169] and/or grade 5 events[163,169,170] yet the heterogeneity within the cohorts and the small patient sample limited the possibilities to draw generalizable conclusions. Comparing the results from other analyses with those from our study remains difficult since some analyses included both CFRT and SBRT treatments [163-166] and some analyses also included both re-irradiated in-field and out-of-field recurrences[162,167,168,170]. Of interest here was the finding that toxicity was less pronounced for the subgroup of patients within the cohorts treated for in-field-failure when compared to those treated with an out-of-field failure[162,167]. This is a significant finding since 72% of the patients in study I had received

additional SBRT-courses for other thoracic targets, which may have impacted the development of side effects. Noted risk factors for serious toxicity in study I were large CTV, central localization and short ΔT. Central location and large tumor volumes are known risk factors both for SBRT upfront[4] and in the reirradiation setting[168,169]. Our findings of increased risk for serious toxicity with shorter ΔT could be possibly explained by the decreased time for repair between the treatments.

Another question to focus on then is which dose-volume parameter was the best predictor for toxicity at reirradiation with SBRT. As mentioned before, there were a variety of different dose-volume parameters associated with pulmonary toxicity, MLD and V_{20} being the most frequently addressed. This study used MLD by summing up the MLDs from the first irradiation, the re-irradiation and if applicable, any other SBRT-treatments delivered at any point of time before the reirradiation. The background was the anticipated toxicity in form of radiation pneumonitis, which has been correlated to MLD[84,87,89]. We were not able to confirm a statistical correlation between lung toxicity grade 3-5 and MLD, yet in light of the diverse nature of the recorded serious toxicity in our analysis, this was nevertheless not to be expected. However, an interesting finding from another analysis found that dose to the heart was statistically correlated to clinical pneumonitis in a patient cohort with reirradiated centrally located tumors[169]. This was reflective of the complexity of toxicity and the clinical as well as dosimetric risk factors.

Apart from the limitations due to the retrospective nature of the study, as described in section 3.2.1.1, there are further points to be considered when interpreting the results. First reconstructing doses in a reliable way to different OAR was not possible, but would have been preferred, especially when considering grade 4-5 toxic events. Secondly, the heterogeneity in the patient cohort with different fractionation schedules, a wide range of different BED and a wide range of tumor sizes has limited the statistics and possibility to draw general conclusions from this collected material. Thirdly, the limited follow-up of the patients may have hidden late presenting effects. Fourthly, patient related factors that could have influenced toxicity (PS, other comorbidities, the extent of metastatic disease) were not recorded. Considering these limitations, one may question if the results from our analysis are applicable for patients who received re-treatment with SBRT in general. This study's major finding that emanates here was the feasibility of reirradiation for peripherally located tumors; whereas centrally located tumors have had a higher frequency of serious toxicity and re-irradiation of these should only be performed after careful consideration of the possible toxic effects.

3.2.1.3 Toxicity presenting after more than 3 years post treatment – Study II

The main aim with study II was to evaluate long-term effects of SBRT, defined as presenting >36 months. At three years, 34 patients were at risk for toxicity and 3 of them developed grade 3 symptoms possibly related to SBRT. The symptoms consisted of rib fracture at 36.8 months, ventricle tachycardia at 38.9 months and dyspnea at 59 months post treatment. The patient developing rib fracture, received a maximum dose to the rib of 56 Gy ($BED_{3,max}$

404Gy). The other patients with grade 3 late effects both received additional SBRT-treatments; the former with a significant history of heart disorders including arrhythmia and 0.3cc of the heart exceeding our local maximum dose guideline to the heart during the second treatment. Late presenting rib fractures excepted, reported late grade 2 side effects ranged between 3-9% in frequency (COPD-exacerbations, cough, dyspnea, exudates, lung infection, upper airway infection), which ought to have been an acceptable level considering a high likelihood to be cured.

At the time of treatment of these patients (2003-2005) there were no dose-constraints for the rib cage or the chest wall, 7% and 4% of the patients experienced ≥ grade 2 chest-wall pain and rib fractures respectively within 3 years, comparable to the other reports. However, rib fractures ≥ grade 2 presenting after 3 years occurred in 18% of the patients at risk, and may have been avoided with today's dose restrictions to the chest wall. Pulmonary function changes are of major interest, yet unfortunately only a few patients had made PFT:s after 2 years (13 patients at 24 months and 8 patients at 36 months), making data scarce for evaluating the cohort on long-term effects. It is also noteworthy, that in addition to this study treatment, six patients (all surviving >36 months) received additional SBRT treatments to the lung that could have been an influence on their development of side effects.

Reports on long-term toxicity post SBRT were scarce and complicated with symptoms from other intercurrent diseases. As concluded from our collected material, the most important message here showing that there was no increase in late-presenting toxicity. This is in line with the recently presented material from long term follow up of the RTOG 0236 trial[34].

3.2.2 Abdominal toxicity

3.2.2.1 General abdominal toxicity in study III

Study III addresses abdominal toxicity, the most commonly noted being grade 1-2 abdominal pain, grade 1-2 fatigue and grade 1-2 nausea, which was comparable to other reports on toxicity post SBRT of abdominal targets[145,146]. Grade 3 toxicity was recorded eight times in seven patients and grade 4 two times in one patient (duodenal ulcer and GI-bleeding), i. e 12% of the patient cohort suffered grade 3-4 side effects. Grade 3-4 toxicity presented either very early ≤3.1 months (5 patients) or very late, >3.5 years (2 patients) post treatment. However, both patients with late-presenting toxicity and the one patient experiencing grade 4 toxicity also received additional radiotherapy towards abdominal targets which may have influenced the toxic effects. The dose contributions from these additional radiotherapy regimens have been reported separately, with no intention of creating summations of doses to the organs at risk. The reason behind constitutes the uncertainty in assessing normal tissue repair (other radiotherapy treatments for patients with ≥grade 3 intestinal toxic effects were given between 7.5-30 months from the study treatment) and the uncertainty in evaluating which parts of the OAR were being affected with significant dosages.

Eight patients experienced pain or symptoms of pressure from their adrenal metastasis prior to treatment, and four of them responded to treatment, two did not respond to treatment and two were not evaluable for assessment of symptom response.

3.2.2.2 Toxicity in the gastrointestinal tract

Toxicity of SBRT of adrenal metastases has generally been mild and our frequency of ≥grade 3 toxicity was higher when compared to other analyses; 12% vs 0%[67-75], with the exception of one report where grade 3 toxicity, was scored 6 times in a patient cohort comprising 26 patients, however, five of the toxic effects being hematological[76]. In comparison to gastrointestinal toxicity of other abdominal targets post SBRT, the most commonly reported grade 2 symptoms consisted of abdominal pain, nausea and vomiting and correspondingly for grade 3 effects gastrointestinal perforations, nausea and diarrhea[145,146]. The types of reported symptoms were similar to ours. Plausible explanations to our increased frequency of serious toxicity were doses to OAR and patient related factors. In addition, four of the patients in study III suffered from symptoms of a general character that may be hard to attribute to a specific organ system.

To assess doses to the GI-OAR, we evaluated dose to the stomach and the small bowel for those patients clinically regarded as being at risk for toxicity (defined as the metastasis being localized ≤ 1cm to a GI-OAR). In summary, 14 patients without grade 3-4 side effects had tumors in close proximity to the stomach, 13 to the duodenum and 16 to the small bowel. Only one patient had a target located close to the colon. All patients with grade 3-4 side effects had at least one GI-OAR located ≤ 1 cm of the treated adrenal metastasis. This study evaluated D_{max} and D_{5cc} based on our local guidelines and the QUANTEC-report from 2010[149]. Our local guide lines recommend $D_{5cc} \leq 23.7$Gy (3 fractions, stomach and intestines) and the QUANTEC-report recommends for the stomach $D_{max} \leq 22.5$Gy to approximately 5cc or 4% and D_{max}<30Gy (3 fractions); and to the small bowel D_{max} < 30Gy (3-5 fractions)[149]. Four patients of the twenty-seven who exceeded the QUANTEC-recommendations in study III, developed grade 3 toxicity (weight loss, abdominal pain, loss of appetite, nausea, duodenal stenosis). Both patients with late-presenting serious side effects (abdominal pain and duodenal stenosis) received doses far overruling the expected tolerance level of the respective OAR, whereas only 2 of the patients with early presenting grade 3-4 toxicity received high doses to the OAR. This lack of dose response has posed questions on the accuracy of the side effect grading and its relation to SBRT, the possibility of faulty dose-constraints and the possible effect of other contributing factors such as miss of target and the unintended administration of potential radiosensitizers. The impact on side effects from the low-dose region, affecting larger parts of the intestines or stomach has not been addressed in this analysis and there is a need for further elucidation.

Patients included in study III all had metastatic disease and 55% and 59% received systemic therapy before and after SBRT-adrenal respectively. No patient purposely received

chemotherapy concurrently with the study treatment. However, a duodenal ulcer diagnosed with gastroduodenoscopy approximately one month post SBRT and complicated with bleeding grade 4, evolved in a patient receiving low doses to the duodenum. This patient also suffered from diabetes, medicated with cortisone and immunosuppressants due to a liver transplantation and received chemotherapy at the time of the side effect, possibly making him more vulnerable to toxic symptoms. There was also an uncertainty in the chart as to whether the patient temporarily stopped with chemotherapy at the time of SBRT. This is of course a complicating matter since such systemic agents may add to the risk of toxicity; either causing GI-toxicity themselves or function as radiosensitizers for both tumor and normal tissue. Gemcitabine is a chemotherapeutic agent and known radiosensitizer, frequently used in the treatment of pancreatic cancer. Treating pancreatic cancer with the sequential combination of single fraction (25Gy) SBRT and 1-9 cycles of gemcitabine resulted in the development of late toxicity (def. as ≥ 3 months) with GI-ulcers in as much as 44% of the patients[171]. In contrast, two other analyses of 1-3 fractions of SBRT and sequential gemcitabine for pancreatic cancer, found a lower frequency of late GI-toxicity with grade 2-4 events occurring in 15% [172] and 6% [173] of the patients respectively. It is worth pointing out that all three analyses had strict dose constraints to the duodenum, however not published in the first report why comparison of doses is impossible. A case report from Japan also highlights the possible elevated risk for toxicity with the combination of SBRT and chemotherapy[174]. In addition to traditional chemotherapy there are anticancer agents with different mechanisms of action which may affect the outcome of radiotherapy. The administration of bevacizumab or Sorafenib, both VEGF-inhibitors, prior and/or post SBRT for abdominal lesions, resulted in 35% of the patients with VEGFi, developing grade 3-5 bowel toxicity, why the authors concluded that other therapies than SBRT may be used if treatment with VEGFi in the near future is likely[175].

Another characteristic worth taking into consideration is that the stomach and the intestines are highly mobile structures also affected in shapes and volumes by their contents at the time of treatment. Currently, when treating adrenal metastases fiducial markers were used, placed in the vicinity of the target, for image guidance and the patients were treated on an empty stomach. Historically, this has not always been the case, leaving room for set-up errors and inter-fraction movements. On the other hand, treating tumors in the SBF has resulted in high grade of local control in clinical evaluations of the method[6,42]. Another aspect is the movement of the target itself. When treating adrenal metastases, Katoh et al[71] looked at the movement of a fiducial marker placed in the vicinity of the adrenal and concluded that it moved <1cm in the supine position, though the treatment technique was different to ours.

Interpreting toxic effects in a heavily metastasized patient cohort is delicate. Toxic symptoms may be both under- and over reported (as described in section 3.2.1.1) due to general cancer morbidity symptoms. The majority of the reported serious toxicity was such general symptoms (fatigue, nausea, weight loss, loss of appetite and vomiting), which may have been caused by the cancer itself or by other antitumor agents. The heterogeneity between the presented symptoms limited the statistical testing of any differences.

3.2.2.3 Kidney toxicity

We experienced two complicating situations when addressing kidney toxicity; the first being that eight patients only had one functional kidney due to nephrectomy, and the other one being four patients who received bilateral treatments for adrenal metastases. Doses to the kidney would preferably be described as a dose to the ipsilateral and contralateral kidney respectively, yet due to the above-mentioned situations, we instead considered the kidneys as one OAR and evaluated doses to total kidney volume for each patient. During follow-up, we could not confirm any kidney toxicity or increase in S-creatinine of >50% as compared to the baseline value at three (n=35) and six months (n=33) post SBRT respectively. This was neither to have been expected since $V_{BED3,40Gy}$ (the currently used dose-volume parameter) to the total kidney volume was limited. Our finding is in line with the findings from Svedman et al[176] who investigated seven patients, treated with SBRT to a single functioning kidney. None of these patients experienced kidney toxicity and V_{15Gy} was kept <40% for three or four fractions in all patients.

3.2.2.4 Adrenal insufficiency

Study III addresses adrenal insufficiency, which was noted in five patients (4 with grade 2 and 1 with grade 1) after a median of 4.1 months (0-94.2). Interpreting adrenal insufficiency in a retrospective cohort with patients with spread cancer was complicated due to the similar nature of both general cancer morbidity symptoms such as fatigue, low blood pressure and electrolyte disturbances, and symptoms of adrenal failure. Therefore, the grading of adrenal insufficiency in study no III, was based on the diagnosis made by the treating physician. No routine assessment of adrenal insufficiency was performed in the clinic and for the three patients who performed an ACTH-stimulation test, their test scores fell out of the normal.

Another concerning issue was that cases with adrenal insufficiency may have remained undiagnosed, since 19 patients had cortisone treatment due to another indication (brain metastases, generally invigorating or other). The most important future aspect is to foresee which patients are at risk for SBRT-induced adrenal insufficiency. Theoretically, based on the principle that clinical symptoms appear when >90% of the cortices of the adrenal glands[66,150] are lost, one might imagine that three categories of patients would be at greatest risk of this side effect; 1) patients receiving SBRT bilaterally, 2) patients with only one functioning adrenal gland receiving SBRT towards that, 3) patients with metastatic disease in both adrenals and receiving unilateral SBRT. We looked at those categories in study no III (table VII). Fourteen patients belonged to either of these groups and 3 of them developed grade 2 adrenal insufficiency (i.e requiring substitution therapy). For the remaining eleven patients in these risk groups, four had cortisone treatment which may have hidden the side effect, but otherwise we could not confirm any particular reason for why adrenal insufficiency did not develop (7 patients received >94Gy (BED_{10}) to 98% of the CTV, median FU was 12.9 months (2.6-75.1), tumor location was right sided (n=5), left sided (n=4) and bilateral (n=2).

Finally, forty-four patients received radiotherapy to treat one adrenal metastasis with the other adrenal gland being intact and two of them had still developed adrenal insufficiency. In surgical material 22% of the operated patients developed symptomatic adrenal insufficiency post adrenalectomy; obesitas, hypertension, diabetes and large tumor size had been risk factors[177]. Further addressing this issue in a prospective trial, assessing adrenal functioning biochemically and clinically regularly post SBRT, is a necessary next step.

Table VII Irradiation towards adrenal tissue

	No of patients	Adrenal insufficiency
SBRT of all adrenal tissue		
Bilateral metastases – SBRT of both	4	G2: 2
Bilateral metastases – SBRT of one	8	G2: 1
Unilateral metastasis – single adrenal gland	2	-
SBRT with functioning adrenal tissue remaining		
Unilateral metastasis – two adrenal glands	44	G1: 1 G2: 1

G1: grade 1. G2: grade 2.

3.2.3 Radiation induced brachial plexopathy

Radiation induced brachial plexopathy (RIBP) was assessed in study IV, where it was noted in seven patients; grade 3 in four patients and grade 2 in three patients with the first symptom presenting after a median of 5.8 months (0.7-12.9) and the worst grade after 8.7 months (6.1-30.6). None of these patients received neurotoxic chemotherapy, had local failure or diabetes as potential contributors to the development of their side effects. The three worst affected patients (fig 7), diagnosed with neurophysiological examinations, had severely handicapping symptoms with pain, sensory and motor alteration. Those patients with pain were clinically diagnosed and one of them had symptoms showing improvement over time and one patient only suffered pain on one occasion. However, apart from the study treatment, three patients in the cohort also received significant doses to the brachial plexus from additional radiotherapy treatments, one of them had developed grade 3 RIBP. Interestingly, when reviewing the dose-plans for the patients with RIBP, the patients suffering from the most severe symptoms had all received high doses affecting the entire circumference of the plexus for several centimeters whereas 8 of the 10 patients receiving $BED_{3,max}$ >130Gy and had not developed RIBP, only received the dose along with the structure, not affecting the entire circumference.

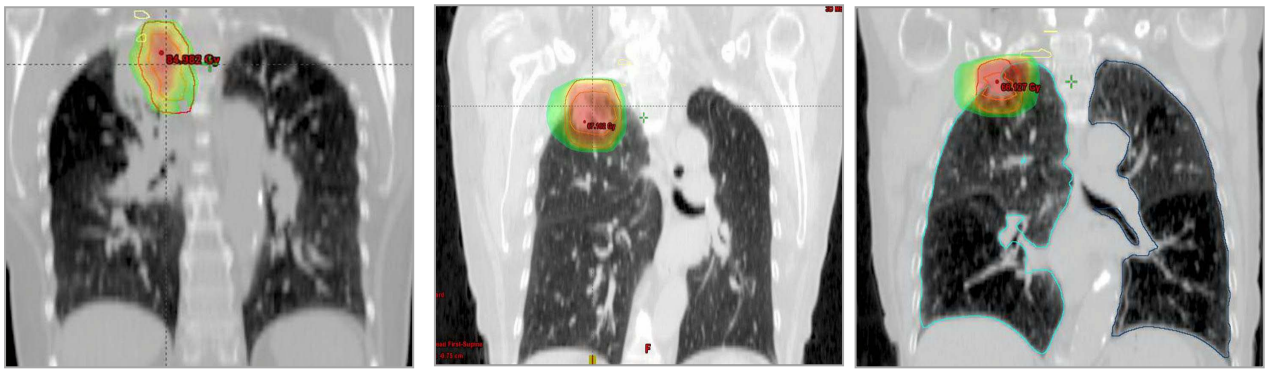


Figure 7: Doses in color wash exceeding BED_3 130Gy for the three patients suffering from serious RIBP (motor and/or sensory affection).

As mentioned in the introduction, the largest analysis of SBRT-induced RIBP constituted the analysis from Forquer et al[136] who, based on 37 treatments and seven cases with grade 2-4 RIBP, concluded that D_{max} to the brachial plexus should be < 26 Gy for a 3-4-fraction-treatment. However, two other analysis, one on SBRT-material and one on CFRT had suggested higher dose restrictions of D_{max} ≤35 Gy and V_{30Gy}≤0.2cc (4 fractions)[116] and D_{max} ≤78Gy and V_{76Gy}≤1cc (CFRT)[132] respectively. The latter pointed out the importance of achieving local control to avoid the possible effect of a local failure, causing tumor induced brachial plexopathy which may be even more disabling[132].

Also of note in study IV was its being compromised with limitations similar to the other studies i.e retrospective materials, heterogeneity within the cohort, uncertainties in addressing toxicity, small patient cohorts and limited number of patients presenting symptoms etc. However, in addition, there were also limitations specific for study IV. Firstly, there are treatment related uncertainties such as the impossibility to correct for absorbed doses to the plexus from other radiotherapy treatments and the fact that we do not use hard dose constraints to this structure, yet over the years an increased awareness of this OAR has been noted. Secondly, D_{max} to the plexus refers to a very specific point and in a fine structure like the brachial plexus which follows the lung almost horizontally; there were uncertainties as to whether the location of D_{max} from the dose-planning CT was representative for the location of D_{max} during treatment. Apart from set-up-errors and intra-fraction movement, uncertainty which also prevailed in the delineation of the structure as pointed out by a validation analysis of the RTOG-contouring atlas[178]. These were all issues to be born in mind when interpreting the created NTCP-model (fig 8) as well as the general fact that NTCP-modeling does not accurately describe the dose-distribution within the organ.

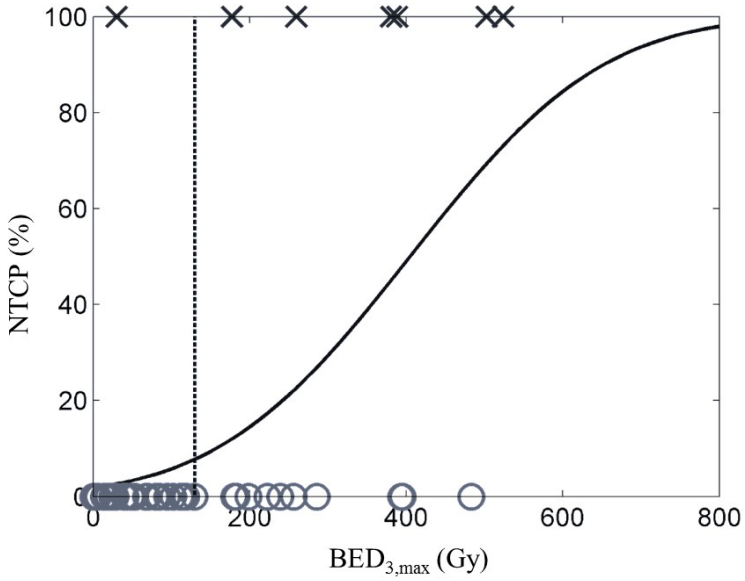


Figure 8: NTCP-modelling for $BED_{3,max.}$ Crosses represent patients with RIBP and rings represent patients not developing RIBP. The dotted line shows the level of $BED_{3,max}$ 130Gy, AUC 0.87.

In study IV, the $BED_{3,max}$ NTCP model showed the best fit of the data (fig 8). Considering the prediction by the NTCP-model as well as aforementioned uncertainties, we suggest to increase the dose-constraint to the brachial plexus to $D_{max} \leq 30$Gy for three fractions.

3.3 LOCAL FAILURE

3.3.1.1 Local recurrences after reirradiation – study I

Local control of SBRT was high, yet when considering the increasing number of patients being treated with this method, the absolute number of local failures will be on the increase. How should such local failures be treated? Technically, surgery remains one option. However, in spite of the favorable outcomes with long term survival, high rate of local control and limited toxicity reported in small patient cohorts treated with salvage surgery (most often lobectomy) of local failures post SBRT[179-181], this alternative is seldom an option for patients previously deemed medically inoperable. Retreatment of a local failure of SBRT with CFRT with 60-70Gy in 30-35 fractions have been described with low toxicity but also a disappointingly low local-progression-free survival of 34% at 1 year, thus questioning the benefit of this treatment[182]. Further alternatives comprise systemic therapy, observation only and retreatment with another course of SBRT. SBRT has the advantage over CFRT of smaller treatment margins, a rapid dose fall-off minimizing the dosage to normal tissue, higher treatment doses and shorter overall treatment time. These advantages can be utilized in the retreatment setting both of local failures after SBRT and after CFRT.

In study I – evaluating reirradiation with SBRT after prior SBRT of a lung target, eight patients progressed locally and six patients could not be properly evaluated. This resulted in 52% of the patients achieving local control at 5 months. This is a remarkably low number in

the context of SBRT and in comparison to our own material with a 92% local control rate at 3 years [6] and 79% at 5 years (study II) using the same technique. Here it is important to remember that the patients in study I were treated in the early era of SBRT when normal radiological changes post SBRT were not well known and bulky fibrosis could be easily mistaken for a relapse. At data collection for the study, the radiological pictures during follow-up were often unretrievable due to the long timelapses, when local control was based on historical radiological statements made in the everyday clinic. The tumors suffering local failure were metastases from NSCLC (n=4), CRC (n=3) and hepatocellular carcinoma (n=1) and only two of them received BED >100 Gy (prescribed dose 15Gyx3) at re-irradiation. A general comparison between local control after SBRT upfront versus SBRT as re-irradiation after prior SBRT, revealed poorer local control with 22-40%[161,162,166] of the patients having relapsed within 9 months post re-irradiation [162,166]. Possible explanations to these inferior results might result from the underlying tumor biology with survival of radio resistant cell clones after the first treatment and rearrangement of the tissue structure after the first ir-radiation, which might cause increased hypoxia. From our analysis, it was also noted that the SBRT doses generally were low (only 6 of the 32 tumors had prescribed BED >100Gy at the re-irradiation). Yet another question was the magnitude of the actual delivered dose to the tumor, considering among other things the lack of image guidance at this point of time

3.3.1.2 Late presenting local failures – study II

In study II – focusing on late presenting relapses, we reported seven local recurrences during the entire follow-up time (table VIII); four occurred within 3 years and three after three years. At present, there is a growing body of evidence for late effects of SBRT with generally high 5-year-local control rates after SBRT between 78%-90% [36,37,39,87,90,183], and subanalyses from some of the cohorts showing superior results for small tumors [37,39,87]. The most recently presented long-term results with a median follow-up 4.0 years, comes from the RTOG 0236-trial, reporting a 5-year-local control rate of 93% after SBRT 18Gyx3 (BED_{10}=151.2Gy)[34]. In comparison, our 5-year-local control rate of 79% was in the lower range and finding one single explanation for this would be complicated since local control does rely on several different parameters, partly influencing one another. Risk factors for early local relapse included big tumor size[37,87,184] and lower treatment doses[39,185,186]. Risk factors for late local relapses have not been established and may differ due to other biological mechanisms and interactions between the host and the tumor. First, looking at dose-volumetric data from reports with 5-year-local control rates at ~90%[34,36,90], the majority of their patients did receive somewhat higher doses (BED_{10} 105-151Gy) as compared to our cohort, while at the same time, the proportion of T2-tumors was higher in two studies[36,90] . Increasing the dose may increase both local control[186] and, for T2-tumors, survival [187]. Second, the refinement of the SBRT-technique in recent years with improvement in dose calculations, geometrical verification and tumor movement assessment has hopefully improved treatment outcome, although uncertainity still remains. Taking these factors into consideration, one might still hypothesize that our standard dose (15Gyx3 corresponding to BED_{10} of 112.5Gy) might be

too low, especially for large tumors that have more tumor cells to kill off and also may be more radioresistant due to hypoxic areas.

Another interesting aspect concerns which type of tumors that recur after several years and what mechanism lie behind this. Unfortunately, only a few reports describe the characteristics of the tumors relapsing after >3years (table VIII) however one interesting finding is that tumors who relapse later are T1-tumors[41,42]. However, drawing specific conclusions from the limited number of cases from these three cohorts (table VIII) is difficult; T2-tumors comprised 60%[42] of the tumors in one study, but only ~28% in the other two[41], why fewer patients with large tumors were at higher risk from the beginning. Another aspect is the negative influence on survival from large tumors, reducing the number of patients at risk at later times for evaluation. In study II in this thesis, such a relation could however not be verified. Another interesting aspect is that even after surgery, where the entire tumor lesion is removed, 9% of the recurrences after surgical resection of NSCLC occur after 5 years, 1% being local recurrences[18]. Thus, it is important to understand more of the biology of late presenting relapses, especially when applying SBRT to operable patients where long-term survival is expected. Biopsies before treatment and at suspicion of local failure are important to understand more of the underlying mechanism.

Table VIII Characteristics in early and late local relapses

Study	**Dose**	**Early local relapses ≤36 m**			**Late local relapses >36 m**		
	(BED_{10}) *Gy*	T-stage	Number *n*	Time *m*	T-stage	Number *n*	Time *m*
Baumann 2006[42]	60-120	T2	13	<36	T1	3	>36-49
Matsuo 2012[41]	105.6	N.S	N.S	N.S	T1	3	101-109
Current study	112.5	T2	4	10-36	T1	3	38-76

N.S: not stipulated

A notable limitation with our study is the diagnostic method of the late local failures (x-ray=1, CT=1, PET=1). No patient was invasively diagnosed which leaves room for questioning the accuracy of the local failures since bulky fibrosis often developed post SBRT. Focusing on late presenting relapses; PET-CT or the presence of ≥3 high risk CT-features (used in 1 patient each) are accurate diagnostic methods[45 44]. Hence, these two late local failures are most certainly true, whereas the local failure diagnosed by just x-ray is highly questionable and probably does represent bulky fibrosis.

Noted risk factors for local recurrence throughout the observation period were large tumor size, probably reflecting the insufficient dose in relation to tumor size, and the finding that 57% of the local relapses were located in the lower lobes, possibly reflecting a relative under dosage of the target due to large breathing motions.

3.3.1.3 Local control of adrenal lesions – study III

Study III shows local control rates of 92% and 87% at 1 and 2 years respectively which is comparable to[67,68,71,76] or superior[69,70,72-75] to other reports. Five patients with six tumors experienced local failures after a median of 8.2 months; two came from rectal cancer, three from NSCLC and one from malignant melanoma. Risk factors for local recurrences were large tumor volume and lower doses. Due to differing risk situations and various local protocols, the patients in study III were treated with a variety of fractionation schedules resulting in 17% of the patients having prescription doses of BED_{10} <58Gy, 21% between 58Gy-70Gy, 41% between 71-99Gy and 21% > 99Gy. There was a tendency towards poorer coverage of doses for cases with local failures as compared to cases with local control (fig 9).

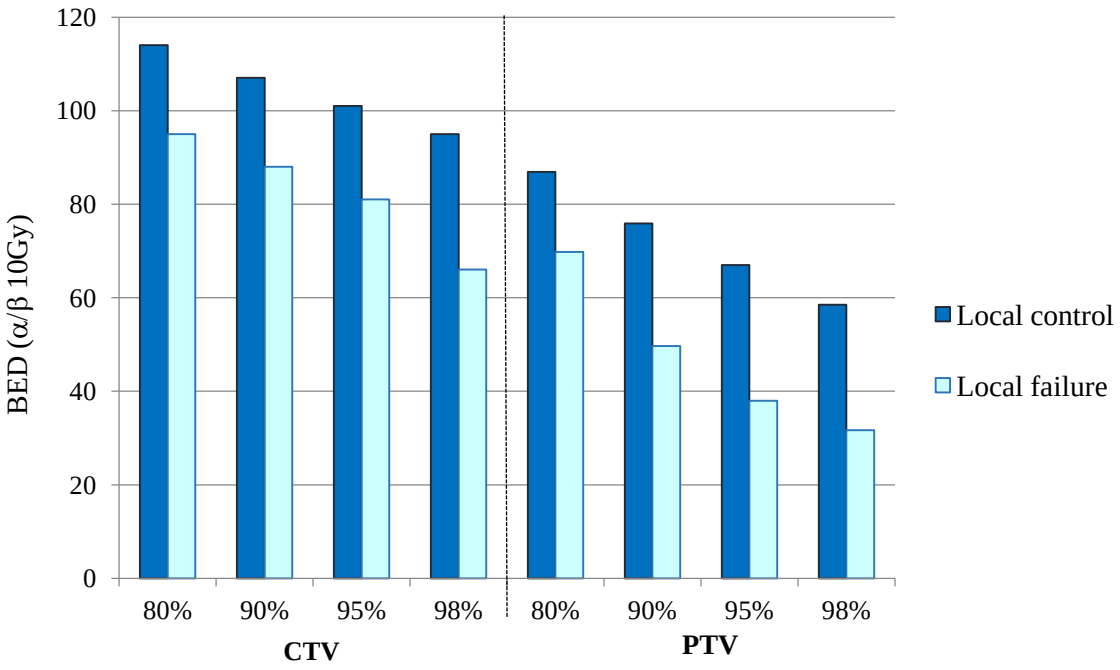


Figure 9: Doses in BED_{10} covering 80-98% of the CTV and PTV for cases with local control and local failure respectively in study III. There was a tendency for poorer coverage of doses for the cases with local failures as compared to the cases with local control.

3.3.1.4 Shortcoming in assessing local control

There are uncertainties in the assessment of local control in the studies of this thesis (study I, II, III). First, the lack of cytological/histological confirmation or PET-CT when local failure was suspected is notable limitations. For a pulmonary target suspicious of failure,

transthoracic needle biopsy was in many cases not a viable diagnostic option due to reduced lung capacity of patients with COPD. In this situation, PET-CT had a sensitivity and specificity of 100% to reveal a local failure[45], but was less common in the early 21st century when these patients were treated and followed. The occurrence of ≥3 high-risk CT- with features for local recurrence has a sensitivity and specificity of >90%[44] and may be a feasible option for evaluation of local control within the studies I and II and relevant cases in study IV. However, if possible a local recurrence in the lung should be confirmed, preferably by histology/cytology and if this is not possible, by a PET-CT. In study III (adrenal metastases), judging local control is less complicated since bulky fibrosis does not blur the picture. A dedicated radiologist performed the evaluations in study II and III, which strengthens our diagnostic accuracy.

Second, study I and III are also compromised with the uncertainty on the malignant potential of the lesion prior to SBRT that may have affected the later evaluation of local control. In study I, one might possibly suspect that a bulky radiation fibrosis in the early era of SBRT could be mistaken for a local failure, which was the indication for re-irradiation. In study III (adrenal metastases), 28 tumors were diagnosed as metastatic lesions by CT-examinations, evaluated in the everyday clinic. Although, assessed by experienced radiologists, we did not reevaluate the lesions for typical signs of malignancy prior to SBRT (described in introduction), why local control of these lesions might be questionable. Overall, some metastatic patients received other anti-cancer therapy, possibly affecting local control of the SBRT-treated lesion. These two last shortcomings are mainly due to the retrospective nature of the studies.

3.4 OUT-OF-FIELD FAILURE

Study II addresses out-of-field failures, whereas the other studies did not due to the metastatic state of the patients and the wide variety of histology and primary tumors. Out-of-field failures occurred in 15 patients (26%) as first presentation of failure, 11 of them presenting within 36 months. During the entire follow-up period, when the out-of-field failures are subdivided into regional failure and distant failure, 7 patients were diagnosed with regional relapse and 15 patients with distant metastases at some time during follow-up, both appearing after a median of 25 months (2.9-84.4) respectively.

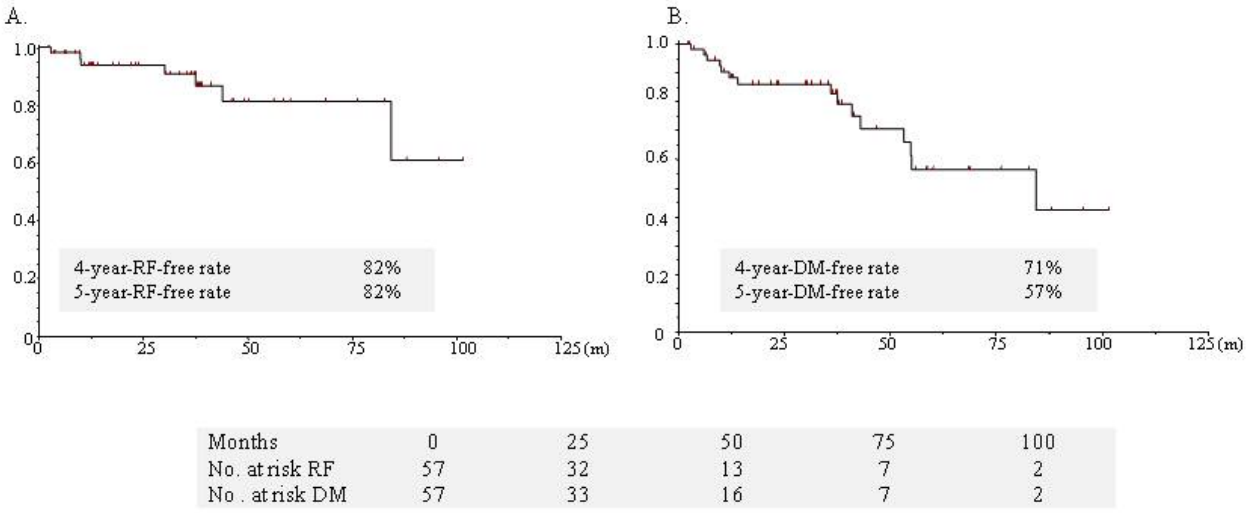


Figure 10: KM-analyses (study II) of A) Regional failure and B) Distant failure.

The impact of tumor size on tumor progression has not been fully elucidated yet. Large tumor volume is a risk factor for systemic progression which to some extent is supported by our finding of shorter time to progression according to tumor stage, which is in accordance to the reports of others. However, PET-CT became a standard procedure in the diagnostic work-up for early stage NSCLC during the inclusion period of the study, and only 18 patients (32%) in the cohort underwent an ^{18}F-FDG-PET for cancer staging, leaving a possibility that disseminated disease already existed at diagnosis. Improving the diagnostic accuracy of staging is one of the great challenges in treating NSCLC.

In patients with suspected or proven potentially resectable NSCLC, a randomized trial showed that PET-CT followed by further invasive diagnostic or therapeutic procedures led to the upstaging of 27% of the patients as compared to 12% of the patients doing invasive diagnostic or therapeutic procedures[43]. Diagnosis of a suspected relapse is equally important, but invasive diagnosis may also in this situation be afflicted with technically complications, especially when the suspected lesion is located in the lung.

3.5 SURVIVAL

3.5.1 Stage I NSCLC – study II

In study II we noted a disappointingly low overall survival rate at 4 and 5 years, of 39% and 30% respectively, which is somewhat compensated by the cancer specific survival of 82% and 74% at the corresponding time points. Seven patients were alive at the time of the analysis fourteen patients were deceased due to lung cancer and 36 due to intercurrent disease. Three questions that arise are if SBRT has contributed to the limited survival of the patients, which risk factors can be identified for decreased overall survival and if these patients did receive any benefits from the treatment or not.

The five-year-overall survival rate post SBRT for medically inoperable NSCLC is in the range of 21-60% [19,38,42,95,183,187] and inferior to the rates of 66-75% reported after surgical resection [18,19]. This is probably a reflection of death due to intercurrent diseases, an assumption further supported by the finding of 5-year-survival rates >80% post SBRT in cohorts with a large proportion of operable patients and/or small tumors[33,188]. It is also supported by the observation that OS has been similar for SBRT and surgery as concluded from results of analyses using matching techniques or adjusting for age and inoperability [19,24,26,27]. In comparison to CFRT of early stage NSCLC the estimated 5-year-survival from CFRT is historically very low, about 21%[29]. However, the SPACE-trial, randomizing medically inoperable patients in the 21st centrury between CFRT and SBRT, could not affirm any differences in survival between the treatments[189]. This result may mirror the improvement of radiotherapy in general, but it should also be noted that toxicity and convenience for the patient were in favor of SBRT in the SPACE-trial. In study II, 65% of the patients were inoperable due to COPD that is a life threatening illness. Patients with COPD all stages have an expected 5-year survival of ~45-73%[190-192]. The low survival rate in study II may therefore not entirely be explained by COPD. Plausible explanations could be the younger age[190,191] and more females[190] in the COPD-studies as well as the contributing effect of other diseases; for example heart-failure has a dismal prognosis with 5-year-survival of approximately 27[193].

Risk factors for inferior survival post SBRT include large tumor volume[38,187,188], CCI ≥ 6[38] and male gender[187] . Another interesting aspect is the radiation dose. Keeping BED_{10} >100Gy has long been associated with improved local control and survival[194]. Recent analyses have shown a significant survival benefit if prescribing doses $BED_{10} \geq 150$Gy for T2-tumors[187], but the results have to be verified prospectively.

Ninety percent of the patients in study II had COPD and/or heart disorders rendering them medically inoperable. There is of course a possibility that damage from radiation may worsen the co-morbidity itself with decreased organ function and shortened life time. However, an interaction between co-morbidity and SBRT with a significant negative influence on survival, has not been confirmed[38]. Neither could two studies addressing the impact of low FEV1 on survival, show a negative influence of poor pulmonary function pretreatment when comparing patients with better and worse performance[110,114]. Similar trends have been observed by other research, possibly reflecting the reason for inoperability – cardiac disease[113]. Another aspect is the age of the patients since 19 patients (33%) in study II were ≥ 80 years old at the time of SBRT possibly affecting survival rates. Overall survival at 3 years for this age group and treatment indication has been reported to only 48% for medically inoperable cases[195]. This low number should not automatically exclude elderly patients from the treatment and it must be weighed against the 2-year-mortality rate of >70% if the cancer is left untreated[27]. In answer to the first question above, it is unlikely that SBRT has contributed to the short survival. The second question is more difficult, low pulmonary function or high age should not isolated preclude the patient from therapy, but the impact of the combination from multiple negative factors needs to be further looked in to.

3.5.2 Metastasized patients – study I and III

The patients in study I and III, comprising metastasized patients, had median survival of 19 and 16 months respectively, which are, but to some extent expected from patients with metastatic spread. The major question in this setting is the basis for delivering an aggressive local therapy with risk of serious toxicity to heavily metastasized patients with expected limited overall survival. In study III, the demographic pattern over time (fig 11) shows that even though increasing the number of absolute treatments, both side effects as well as local recurrences have decreased in frequency, justifying the current treatment patterns.

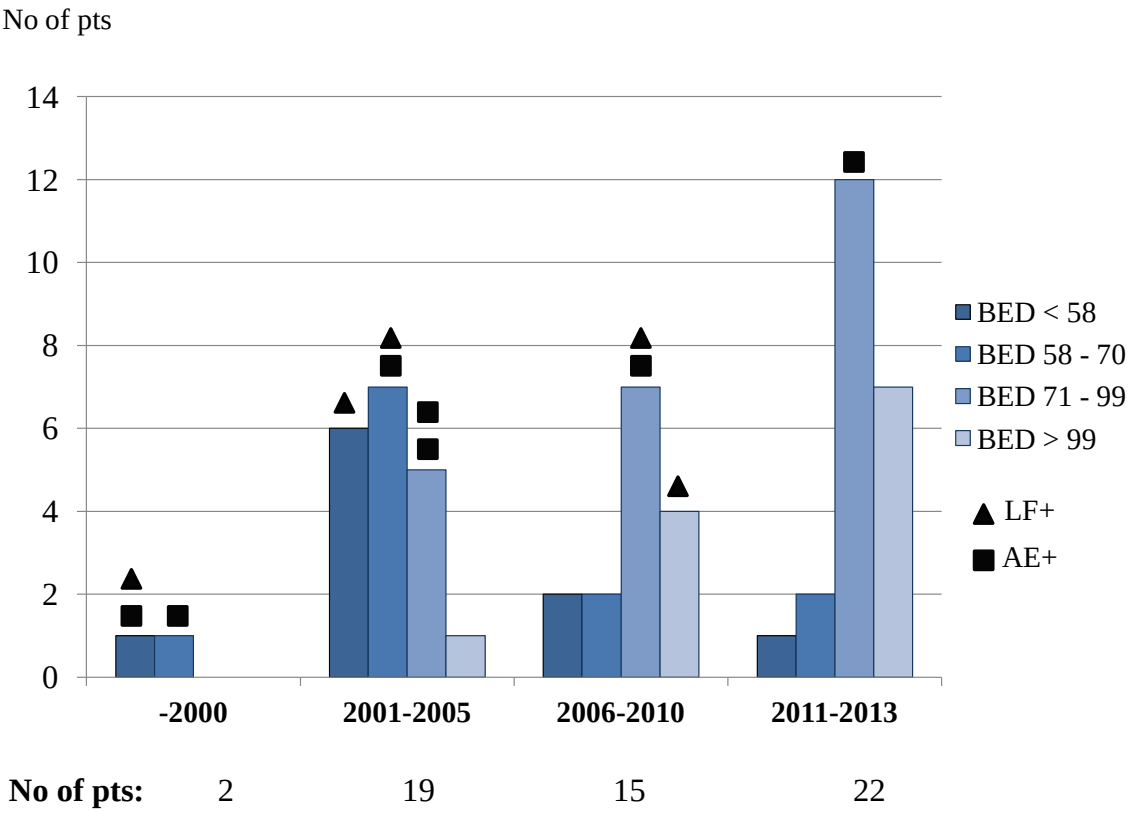


Figure 11: Number of patients treated during different time periods and with different prescribed doses in BED_{10}. Noted local failures (LF+) and grade 3-4 side effects (AE+).

SBRT in the metastatic setting should primarily be considered where untreated metastases may cause severe local cancer morbidity symptoms due to tumor progression or when a high gain in overall treatment effect may be expected, such as the oligometastatic situation. Another special situation is NSCLC with a single adrenal metastasis, in which ablative therapy of the metastasis may achieve favorable outcome with long-time survival[70,72]. A sub-analysis from study III on patients with a single adrenal metastasis versus patients with multiple metastases including an adrenal lesion shows similar promising results.

3.6 FRACTIONATION IN SBRT

The Linear-Quadratic model (LQ-model) describes quantitatively the effects of fractionation that was empirically found in the 1920s. At present, it is commonly used in CFRT in the clinic to convert doses from different fractionation schedules into biologically equivalent doses (BED) to compare the schedules with respect to tumor- and normal tissue effects. Although well validated for small fraction doses, the LQ-model has been questioned for high fraction doses as used in SBRT, due to an overestimation in cell-killing effect for large doses, seen from *in-vitro* data. BED, according to the LQ-model, is based on the values of the total dose (D), the fraction dose (d) and the α/β-value. The α/β-value describes the damaging effect of radiotherapy to the cell; the α-value stands for the cell-specific un-repairable lesions and the β-value represents the cell-specific combination of repairable sublethal lesions. Tumors generally have a high α/β-value whereas a low α/β-value is used to estimate late normal tissue effects. The LQ-model predicts a larger therapeutic window with reduced risk for toxicity when increasing the number of fractions, in correspondence to what is observed in the clinic.

More recently, many centers have more frequently been using an increasing number of fractions in SBRT (sometimes called risk adapted SBRT) from 3 up to about 10, when the tumor is located in close proximity to an OAR. The intention, by this strategy is to spare the normal tissue and avoid any late side effects, and is adopted to SBRT as a direct extrapolation from the experience in CFRT. Advocates of using the LQ-model for high fraction doses point out that results from pre-clinical and clinical data do not support the need to change the LQ-model and that the excellent clinical results with SBRT rest upon the technical possibilities to deliver much larger biologically effective doses[196,197]. However, the validity of LQ at high doses has been questioned by critics based on both *in-vitro* and *in-vivo* experimental data and alternative models have been suggested; for example the Universal Survival Curve model (USC-model)[198] and the generalized linear quadratic model (gLQ-model)[199] . Interestingly, non-LQ models such as USC predicts a larger gain in therapeutic window compared to the LQ model by increasing the number of fractions, at doses commonly used in SBRT[157]. Today, however, conclusive clinical *in-vivo* data from SBRT, supporting a gain in therapeutic window by increasing the number of fractions from a few up to about ten, is still lacking.

In addition to the debate on the role of fractionation in SBRT, there are also theories that completely different mechanisms, not accounted for in radiobiological models, may play an important role; hypoxia, especially in single-fraction SBRT may increase the radioresistance[200], vascular damage from high doses may cause delayed, necrotic cell death which causes the LQ-model to underestimate the cell-killing effect[201] and immunologic effects may activate and attract immune cells that might kill cancer cells or even damage the vasculature[202].

The NTCP-modeling in study IV was done both with the LQ-model and with the USC-model in order to see if there was any difference in predictive power between the two. The USC-

model is a hybrid between the LQ-model (at low doses) and the Single Hit Multitarget model (SHMT) (at high doses), and was constructed with the motivation that the LQ-model works well in the low-dose region whereas the SHMT performs better in the high-dose region[198]. It was developed by Park et al and its goodness-of-fit, tested on NSCLC-cell lines, was superior to that generated from the LQ-model[198]. In the NTCP-modeling in study IV of this thesis, there was no major difference between the models (LQ vs USC) for predicting toxicity. There was no perceived benefit for increased fractionation, but the patient material was limited and the follow-up was short of patients who received "risk-adapted" fractionation schedules. Interestingly though, when treating with SBRT at our institution, the maximum allowed dose to the plexus has historically been decided individually for each patient at the discretion of the treating radiation oncologist. However, since 2011 we have increased the awareness of the brachial plexus as an OAR by routinely segmenting this structure in the planning CT images and occasionally used a "risk adapted strategy" with an eight-fraction-treatment for tumors in close proximity to the plexus. Over this period, no RIBP has been reported, but the evidence for drawing conclusions from such a finding are scarce since the follow-up was limited and the anatomical distribution of the high-dose-region could also play an important role here.

Modeling SBRT-induced toxicity is of major importance. The predictive power of any model is primarily dependent on the input data in the modeling. Thus, there is a future need for data collection, with very well defined end-points for both the modeling and treatment data. Regarding the latter (in study IV), maximum doses are shown to have a higher predictive power, compared to the different volume doses. Error estimates of the maximum doses, i.e. the differences between planned and delivered maximum dose, is not explicitly given but could be expected to be relatively large. Both the definition of the end-point as well as the estimate of the delivered maximum dose should be regarded as limiting factors in this modeling and has highlighted the need for more high quality clinical data in the not-too-distant future.

3.7 WHOM SHOULD BE TREATED WITH SBRT FOR….

3.7.1 Local recurrence after prior SBRT with a new course for SBRT?

Local failure is the most common type of failure observed post reirradiation with SBRT after prior SBRT[161,162], motivating the indication of re-irradiation. However, in light of the reported high rate of serious toxicity from our material, there is a need to more carefully select suitable patients. A patient with a small relapsing peripherally located tumor and a long expected survival or even a chance for cure should be a candidate for re-irradiation. On the contrary, careful consideration should be taken for a patient with a big centrally located tumor with a short interval between the first treatment and relapse before re-irradiation is performed. A more complicated situation occurs when the relapsing tumor is threatening central structures. In these cases careful risk estimation between possible radiation induced side

effects and possible tumor induced symptoms has to be made as well as to consider other treatment options.

3.7.2 Medically inoperable stage I NSCLC?

This patient group has few treatment options and SBRT has emerged as an alternative with high rates of local control, limited side effects, on both long and short sight, and cancer specific survival at 5 years at 74%. Hence, SBRT for these patients remains a good and plausible treatment option and the question here is mainly to identify patients with limited survival due to other causes and patients at risk for high-grade side effects. As discussed previously, severe COPD, low pulmonary function and old age, should isolated not preclude a patient from curative intended SBRT. Instead, to further optimize the basis for treatment decision there is a need to create multi-dimensional-models, based on both dosimetric and patient characteristics, to foresee toxic effects, survival and disease control.

3.7.3 Apically located lung tumors?

With respect to RIBP, apically located lung lesions can be reasonably safely treated as long as the brachial plexus is considered a risk organ that needs careful assessment and accurate delineation. Improving the skills of radiation therapists in delineating the structure is of major importance since sparing of the structure should not unrightfully compromise with coverage of the target, leading to local failure. The NTCP-model predicts <10% probability of grade 2-3 RIBP if $D_{,max} \leq 30Gy$ for three fractions. However, paying attention to the distribution of dose within the plexus as well as to further address the utility of risk adapted SBRT are important future aspects. Today, an apical location of a lung lesion should therefore not exclude a patient from SBRT, but given the results from study IV, it is advisable to restrict $D_{max} \leq 30Gy$ for a three-fraction-treatment.

3.7.4 Adrenal metastasis?

Adrenal metastases can be treated with excellent local control, but in light of the recorded toxicity and the limited survival of the patients as seen in study III, there is a need to distinguish favorable tumor- and patient characteristics for these patients. In terms of tumor characteristics, small tumor volume and right sided location seem favorable, the protective effect of the liver causing the major GI-OAR, the duodenum, only rarely being affected by the high-dose region. Additionally, to evaluate the overall treatment effect in comparison to the risk for side effects, the patient´s general status and the spread of the disease also be taken into consideration. With respect to both the risk of toxicity and the possible gain in overall treatment effect, the best patient is suggested to have limited metastatic spread and a small right-sided tumor located > 1cm from a GI-OAR. Most importantly, the aim should be to deliver an ablative dose with good dose coverage of the target and to keep current dose constraint guidelines for relevant OAR.

4 FUTURE PERSPECTIVES

Given the high performance of SBRT, there are a number of possibilities for further developing this method in order to broaden its long-term implications.

First, local control is important and one question is whether further increasing the doses to the target will result in a clinical detectable increase in local control. Investigating this question with the highest scientific quality standards, such as in a randomized controlled trial, calls for very large patient material to ascertain and show if any of the observed difference is statistically significant or not. Nevertheless, a study comparing different dose-levels in relation to tumor size would be of enormous interest. Increasing the dose to larger tumors for a gain in local control has to be balanced against the possible increase in toxicity. Another side of the same coin is whether or not reducing the dose to small tumors could reduce side effects, but maintain local control, which would be important for tumors in close relation to OAR.

In addition, to carefully assess dose to OAR both retrospectively and prospectively to gain clinical data of side effects is of utmost importance in learning more about the risks of this treatment. At present, current dose constraints may be over- and/or underestimated. At the same time, it is important to further develop the modeling technique estimating the probability of complications. In addition to evaluating the impact of dose-volumetric data to explain toxicity, it is crucial to also incorporate clinical parameters in the prospective analyses. For the long-term perspective, the aim should also be to include information from biomarkers, predicting the individual radiosensitivity. This will include information of genetic polymorphism (SNPs) on genes important for the radiosensitivity of the individual, for tumors to provide the relevant genomic and proteomic profiles and information obtained by different imaging procedures.

Moreover, treatment of metastatic patients is developing and the use of SBRT as an isolated treatment modality has to be reconsidered. Systemic agents with new mechanisms of action increase disease control, but do not always eradicate the entire macroscopic tumor volume. SBRT may in these cases be used as a consolidating treatment, converting a partial tumor response to a complete response. Theoretically, for patients where 2^{nd} and 3^{rd} line treatment normally has very limited effect, SBRT might in these situations improve survival and prolong time to progression substantially. Another situation appears when some cell clones of a tumor develop mechanisms to outwit the systemic medication, making the therapy less effective at a few tumor sites. In these situations SBRT may be used as local treatment to those sites, while maintaining or temporarily holding up the systemic agent, dependent on toxicity profile of the agent. This concept, with SBRT beyond progression, may lead to the extended use of low-toxic systemic therapy or to a “treatment rest” for a patient with high toxic systemic therapy. Both survival and quality of life could be substantially improved.

Last but not least, a very important aspect for the future is to understand the biological changes in the tumor, in the normal tissue and in the patient after SBRT. Therefore, clinical and pre-clinical studies have to be performed in an interdisciplinary way, analyzing findings from the laboratory bench as well as via clinical patient outcomes in order to link the results and data to one another.

5 POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Stereotactic body radiation therapy (SBRT) är en strålbehandlingsteknik som uppfanns på 1990-talet på Karolinska sjukhuset. Vid SBRT ges mycket höga stråldoser, under endast 3-5 fraktioner, mot tumör samt minimal marginal av normalvävnad. Det bestrålade områdets funktion slås ut. Metoden är idag en standardbehandling för medicinsk inoperabel tidig icke-småcellig lungcancer (NSCLC) och har spritts över hela världen tack vare mycket god lokal kontroll (>90%), låg grad av biverkningar samt den korta behandlingstiden vilket gör det bekvämt för patienten (behandling av tidig NSCLC med SBRT tar en vecka i jämförelse med ungefär sju veckor vid konventionell strålbehandling). Patienter med lungcancer som tidigare inte kunde opereras och endast fick konventionell behandling samt ofta hade återfall, kan nu botas.

Projekt 1: Rebestrålning. I frånvaro av andra möjliga behandlingsalternativ har patienter på Karolinska sjukhuset pga lokal tumörprogress erhållit rebestrålning mot tidigare SBRT behandlade lungtumörer. Tjugonio patienter med 32 rebestrålade lungtumörer med olika ursprung analyserades i studien som framför allt syftade till att utvärdera biverkningar. Sammanlagt fick 11 patienter svåra biverkningar och riskfaktorer utgjordes av stor tumör, central lokalisation (dvs nära bronker, hjärta, kärl) och kort tid mellan första behandlingen och rebestrålningen. Sammantaget visar studien att rebestrålning av små tumörer perifert i lungan är en bra behandling, medan patienter med stora centralt belägna tumörer löper risk för svåra biverkningar.

Projekt 2: Långtidsuppföljning av SBRT av tidig NSCLC. SBRT av lokaliserad medicinsk inoperabel NSCLC har visat mycket goda resultat med en lokal kontroll >90% vid 3 år. I dagsläget finns dock begränsade data på långtidseffekterna efter behandlingen – tumörkontroll, sena biverkningar samt radiologiska och fysiologiska förändringar. Studie II är en långtidsuppföljning av en prospektivt insamlad patientgrupp (57 patienter) som tidigare analyserats med avseende på korttidseffekter[5,6]. Långtidsuppföljningen visar fortsatt god kontroll av den behandlade tumören (79% vid 5 år) och få biverkningar som uppkommer efter mer än 3 år efter behandlingen. Tyvärr ser man även att överlevnaden är begränsad i denna patientgrupp (30% vid 5 år), framför allt till följd av andra hjärt- och lung sjukdomar. Resultaten i denna studie stödjer den fortsatta användningen av SBRT för dessa patienter.

Projekt 3: SBRT av binjuremetastaser. Binjuremetastaser är relativt vanliga och ger oftast inga symtom. Standardbehandling (lokalbehandling) utgörs av kirurgi, men alla patienter är inte lämpliga att operera och ett behandlingsalternativ är då SBRT. SBRT har dock inte utvärderats i tillräcklig omfattning på binjuremetastaser för att säkert fastställa att behandlingen gagnar patienten. I denna studie utvärderas den tumörbromsande effekten och ställs i relation till biverkningar hos patienten. Femtioåtta patienter med 62 binjuremetastaser från olika primärtumörer inkluderades från tre olika centra i Europa (Karolinska Stockholm,

VU-Medical Center Amsterdam, Rigshospitalet Köpenhamn). Tumörkontrollen var mycket god (82% vid 2 år), men vi noterade även att 12% av patienterna fick svåra biverkningar vilka framför allt utgjordes av symtom från mag-tarmkanalen. Sammantaget visar studien att man kan få mycket god tumörkontroll efter SBRT av binjuremetastaser, vilket dock måste vägas mot risken för biverkningar. Framtida studier behövs där man utrönar vilka specifika patientgrupper som kan ha större nytta av just den här behandlingen.

Projekt 4: SBRT-inducerad nervskada på plexus brachialis vid behandling av tumörer belägna högt upp i lungan. Vid SBRT av tumörer högt upp i lungan kan ibland plexus brachialis – ett nervplexus som står för armens och handens funktion – vara ett riskorgan. Om stråldoserna mot detta nervplexus blir för höga kan patienten få smärta, känselstörningar och svårigheter att röra arm och hand. Risken för denna biverkan måste dock ställas mot risken för att underbehandla tumören vilket kan orsaka tumörtillväxt som i sin tur ger lokala skador på plexus med mycket svårbehandlade nervsymtom. I dagsläget är det oklart hur mycket strålning dessa nerver tål vid SBRT. Studie IV är en retrospektiv studie av 57 patienter med 61 tumörer i övre delen av lungan. Sju av dessa patienter utvecklade symtom på strålinducerad plexusskada (RIBP). Utifrån dessa data skapade vi en modell för att uppskatta risken för RIBP vid SBRT och vi analyserade fram en maxdos till plexus brachialis (30Gy på 3 fraktioner) som man inte bör överstiga. Vid tolkning av en sådan modell bör man dock ha i åtanke att det även finns andra faktorer (individuell strålkänslighet, andra mediciner, tidigare strålbehandlingar etc) som kan påverka risken för att utveckla denna biverkan.

Sammantaget stödjer resultaten i denna avhandling SBRT som fortsatt behandlingsmetod. Det finns dock flera områden att vidareutveckla t.ex. frågan om dosökning till olika tumörer liksom frågan om kombinationsbehandling med SBRT och systemiska behandlingar. Vidare behöver man analysera effekten av olika doser till såväl tumör som till normalvävnad och relatera detta till såväl kliniska symtom till prekliniska resultat.

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