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SBRT of large tumors and tumors located near organs at risk in the thoracic cavity

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Before the October revolution, Russian Science stood on the edge of the abyss. Since then, it made a huge leap forward.

A Russian joke

Abstract

Stereotactic Body Radiotherapy (SBRT) is a non-invasive ablative radiation therapy developed at Karolinska University Hospital in the early 90-s. Its basic principles are highly focused inhomogeneous dose load with rapid fall of in the periphery of the target, delivered in few fractions with high-doses per fraction. Due to the ability to spare the surrounding healthy structures, the technique allows for deployment of very high radiation doses in the target, yielding high rates of local control to a price of a limited toxicity. However, high fractional doses of SBRT may cause excessive toxicity in case of proximity of a radiation sensitive organ. Likewise, the volume of damaged healthy tissue increases with the volume of the target, which is important in treatment of large tumors. Dose planning in SBRT is a balance between a dose sufficient for tumor control and compliance with dose restrictions for surrounding tissues. The purpose of this thesis is to elucidate key situations of this important trade-off from a radiological and clinical point of view, and contribute to useful guidelines in the SBRT practice.

Paper I, was a single institution retrospective analysis of 52 patients treated for apical lung tumors in proximity of plexus brachialis. A method for contouring of plexus brachialis was established, and the delineation of the organ was performed retrospectively. Clinical data on radiation induced brachial plexopathy was collected. NTCP-modelling was performed based on different dose-volume parameters, showing a high predictive ability for adverse events. The study provided insights into the feasibility of anatomical delineation, and dose constrictions for plexus brachialis.

Paper II, was a retrospective single institutional study of 164 patients with tumors larger than 70 cc treated with at least 8 Gy x 5, located in thorax and abdomen. 70 cc corresponds roughly to a spherical structure of 5.1 cm. Local control and toxicity were primary and secondary aims. Minimal dose to the GTV and histology were predictive for local control in multivariate analyses. The best local control was for renal cell carcinoma while worst for colorectal carcinoma. Seven of the ten patient that suffered from potentially lethal adverse events had tumor located close to central structures in the thorax. The study showed that, when possible to deploy a sufficient irradiation dose without compromising organs at risk, the SBRT might be a good treatment option for large tumors.

Papers III and IV, were analyses of patients with tumors located near central bronchial structures in the thorax. Paper III is a multicenter non-randomized phase II-trial, involving 65

patients with tumors within 1 cm from trachea, main and lobar bronchi, treated with 7Gy x 8. Ten patients experienced possible lethal adverse event, including eights cases of hemoptysis. Distance to main bronchi and dose to main bronchi and distal trachea were the risk factor for bronchial bleeding. A hypothesis was put forward that tumors located more than 1 cm from distal trachea/main bronchus, and given that the main bronchus/trachea receive less that 70-80 Gy EQD2, are relatively safe to treat with the study fractionation. In paper IV, the cohort was expanded with a retrospective multicenter cohort of patients treated in the same way for tumors within 2 cm from the central bronchial tree. In total, there were 232 patients, with 30 possible treatment related deaths. The concept of the most central sensitive bronchi in the hypothesis described above needs to be expanded to also include the intermediate bronchus. Tumor compression of any part of the PBT was associated with treatment related death. The study provided important material and insights for further dose-volume modulations of individual radiation sensitivity of each part of the central bronchial tree.

LIST OF SCIENTIFIC PAPERS

I. 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. Acta Oncol. 2019 Aug;58(8):1178-1186. doi: 10.1080/0284186X.2019.1601255. Epub 2019 May 8.PMID: 31066326

II. **Grozman V**, Onjukka E, Wersäll P, Lax I, Tsakonas G, Nyren S, Lewensohn R, Lindberg K. Extending hypofractionated stereotactic body radiotherapy to toumors larger than 70 cc – effects and side effects. Acta Oncol. 2021 Mar;60(3):305-311. doi: 10.1080/0284186X.2020.1866776. Epub 2021 Jan 15.PMID: 33448899

III. Lindberg K, **Grozman V**, Karlsson K, Lindberg S, Lax I, Wersäll P, Persson GF, Josipovic M, Khalil AA, Moeller DS, Nyman J, Drugge N, Bergström P, Olofsson J, Rogg LV, Ramberg C, Kristiansen C, Jeppesen SS, Nielsen TB, Lödén B, Rosenbrand HO, Engelholm S, Haraldsson A, Billiet C, Lewensohn R. The HILUS-Trial – a Prospective Nordic Multicenter Phase 2 Study of Ultracentral Lung Lung Tumors Treated with Stereotactic Body Radiotherapy. J Thorac Oncol. 2021 Jul;16(7):1200-1210. doi: 10.1016/j.jtho.2021.03.019. Epub 2021 Apr 3.

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PUBLICATIONS NOT INCLUDED IN THESIS

Alagic Z, Diaz Cardenas J, Halldorsson K, **Grozman V**, Wallgren S, Suzuki C, Helmenkamp J, Koskinen SK. Deep learning versus iterative reconstruction algorithm for head CT in trauma. Emerg Radiol. 2022 Jan 5. doi: 10.1007/s10140-021-02012-2. Online ahead of print.

Karlsson K, Lax I, Lindbäck E, **Grozman V**, Lindberg K, Wersäll P, Poludniowski G. Estimation of delivered dose to lung tumours considering setup uncertainties and breathing motion in a cohort of patients treated with stereotactic body radiation therapy. Phys Med. 2021 Aug;88:53-64. doi: 10.1016/j.ejmp.2021.06.015. Epub 2021 Jun 25.PMID: 34175747

Tsakonas G, **Grozman V**, Ekman S. Primary CNS Metastatic BRAF-mutated Lung Adenocarcinoma With Complete Intracranial Responce to BRAF/MEK Inhibition. Clin Lung Cancer. 2020 Nov;21(6):e544-e546. doi: 10.1016/j.cllc.2020.05.006. Epub 2020 May 12.PMID: 32522509

Tendler S, **Grozman V**, Lewensohn R, Tsakonas G, Viktorsson K, De Petris L. Validation of the 8th TNM classification for small-cell lung cancer in a retrospective material from Sweden. Lung Cancer. 2018 Jun;120:75-81. doi: 10.1016/j.lungcan.2018.03.026. Epub 2018 Mar 30.PMID: 29748020

Franzén B, Viktorsson K, Kamali C, Darai-Ramqvist E, **Grozman V**, Arapi V, Hååg P, Kaminskyy VO, Hydbring P, Kanter L, Nyrén S, Ekman S, De Petris L, Lewensohn R. Multiplex immune protein profiling of fine-needle aspirates from patients with a non-small-cell lung cancer reveals signatures associated with PD-L1 expression and tumor stage. Mol Oncol. 2021 Nov;15(11):2941-2957. doi: 10.1002/1878-0261.12952. Epub 2021 May 1.PMID: 33768639

Grozman V, Svensson M, Holmin S, Andersson T, Söderman M. Spinal dural arteriovenous fistula – uncommon, curable cause of paraplegia. Early diagnosis and treatment can result in total symptom regression. Lakartidningen. 2010 Feb 17-23;107(7):440-3.

Contents

1. Introduction 15
1.1. History 15
1.2. Basic conditions for treatment safety 16
1.3. Means of dose prescription and reporting 17
1.4. Indications for SBRT 20
1.5. Local control evaluation and normal post-irradiation process 21
1.6. SBRT and the RECIST criteria 25
1.7. Toxicity 29
1.8. Tumor radiobiology of hypo-fractionated radiotherapy 37
1.9. SBRT and risk of local recurrence 40
2. Aims of the thesis 44
3. Patients, materials and methods 45
3.1. Patient cohorts and study design 45
3.2. Data retrieval 46
3.3. Risk organ delineation 47
3.4. Dose characteristics 48
3.5. Toxicity 50
3.6. Statistical analyses 50
1. Results and discussion 52
1.1. Radiation-induced brachial plexus toxicity after SBRT of apically located lung lesions (Paper I) 52
1.2. Extending hypofractionated stereotactic body radiotherapy to tumours larger than 70cc – effects and side effects (Paper II) 53
1.3. The HILUS-trial – a prospective Nordic multi-center phase II study of ultra-central lung tumors treated with stereotactic body radiotherapy (Paper III) 55
1.4. HILUS III: A pooled analysis of risk factors for toxicity of SBRT of centrally and ultra-centrally located lung tumors (Paper IV) 55
2. Conclusions 57
3. Future Perspectives 58
Acknowledgments 59
References 62

List of abbreviations

α/β	alfa/beta ratio
AUC	area under curve
BED	biologically effective dose
Cc	cubic centimeter
COPD	chronic obstructive pulmonary disease
CR	complete response
CRC	colorectal carcinoma
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTV	clinical target volume
EGFR	epidermal growth factor receptor
EQD2	equivalent dose in 2Gy fractions
FDG	fluorodeoxyglucose
GTV	gross target volume
Gy	gray
HCC	hepatocellular carcinoma
ILD	interstitial lung disease
LC	local control
LQ	linear-quadratic (model)
MRI	magnetic resonance imaging
NSCLC	non-small cell lung cancer
NTCP	normal tissue complication probability
OS	overall survival
PACS	picture archiving and communication system
PBT	proximal bronchial tree
PD1/PDL1	programmed cell death protein 1 / programmed cell death ligand 1
PET	positron emission tomography
PFS	progression free survival

PR	partial response
PRV	planning organ risk volume
PTV	planning target volume
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RILD	radiation induced liver disease
RIBP	radiation induced brachial plexopathy
RP	radiation pneumonitis
RTOG	radiation therapy oncology group
SBRT	stereotactic body radiotherapy
SD	stable disease
SFED	single fraction equivalent dose
SRS	stereotactic radiosurgery
SUV	standardized uptake value
TKI	tyrosine kinase inhibitor
USC	universal survival curve

1. Introduction

1.1. History

Stereotactic Body Radiotherapy (SBRT) is an ablative non-invasive radiation treatment for malignant tumors mainly in thoracic and abdominal cavity, introduced at Karolinska University Hospital in early 90-s by Ingmar Lax and Henric Blomgren (1, 2). SBRT is an extension of Gamma Knife technique (even known as stereotactic radiosurgery, SRS) to extracranial targets. Initially, it was usually delivered with multiple (normally 5-12) coplanar radiation beams, but this technique is now gradually being replaced by one continuous filed produced by a rotating radiation source – so-called modulated arc technique, which allows for even greater geographical dose spread and further lowering of irradiation dose to a single voxel of surrounding healthy tissue (3). Like Gamma Knife, and unlike conventional radiation therapy, SBRT dose plan consists of a very high and mostly strongly heterogeneous intratumoral radiation dose, with a rapid dose decline peripherally of the target, very high dose-per-fraction and reduced number of fractions (usually three to five).

Unlike intracranial targets in Gamma Knife treatment, extracranial targets exhibit a certain degree of motion, along with the respiratory cycle and the heartbeat, but also along with the physiological movements of the bowel and other internal abdominal organs. Extracranial targets are thus more challenging to treat with an external radiation in a precise, high dose manner compared to the intracranial targets. This challenge was handled by Blomgren and Lax through calculation of different localizations of the target in a stereotactic coordinate system, CT verification of target localizations, extended treatment margins and abdominal compression to reduce the respiratory motion (4).

Introduction of a new curative radiotherapy had required a scientific comparison with already existing modalities. Inoperable stage I Non-Small Cell Lung Cancer patients were traditionally treated with conventional hypo-fractionated radiotherapy up to 60 Gy (or lower)

(5), with fractional doses of 2 Gy. This fractionation schedule yields a conformal dose to the tumor of 72 Gy BED (α/β=10), to be compared to an established dose threshold for lung cancer in SBRT of at least 100 Gy to the periphery of the PTV. The historical rates of local control after conventional radiotherapy alone were poor, mostly between 30 and 70% (5, 6). Dose escalation studies that sought to increase the tumor dose to >100 Gy BED (2Gy per fraction up to 90Gy = 108 Gy BED) showed unacceptable toxicity incl. increased mortality rates (7). Currently, the conventional fractionation for stage III NSCLC is 2 Gy per fraction up to 68Gy, yielding a total BED of 81.6 Gy, which is still lower than >100 Gy usually given in SBRT. Normally, this conventional radiation treatment is prescribed for locally advanced NSCLC, and is given in combination with chemotherapy to prevent systemic metastasis and increase the local effect.

The first retrospective analysis of local control in SBRT, showed an 88% local control rate after a median follow up of 33 months (4). In a prospective phase II trial of SBRT for T1 and T2 localized lung cancer conducted in Stockholm, total KM-estimated local control at 3 years was 92%. Several more recent studies have confirmed a local control of around 90-98% for NSCLC when treated with at least 100 Gy BED (α/β=10) (3, 8-11).

1.2. Basic conditions for treatment safety

When the dose per fraction is high, the number of fractions is low, and the geographical dose distribution within the dose plan is heterogeneous, the cost of a mistake increases considerably compared to the multiple fractions and low dose-per-fraction of a conventional radiation treatment. This applies to the risk of local tumor relapse, as well as to the risk of an excessive toxicity due to excessive radiation dose to nearby healthy tissue; a small uncertainty in the dose prescription, an erroneous contouring of the target or a risk organ, as well as a geometrical mistake during the treatment delivery, may cause a significant deviation from the optimal dose distribution over the irradiated area. Several criteria need to be met in the process of planning and delivery of the SBRT to avoid the above listed mistakes.

1) Knowledge of the irradiation sensitivity of the tumor. At present, a few standardized fractionation regimens, with dose coverage of the target, are used for most tumors. However, when difficult trade-offs need to be made between the target coverage and potential side effects, one would ideally need to better understand the general radiation sensitivity of the tumor type, as well as the radiation sensitivity of the individual tumor and its different sub-volumes. There may be some specific parts of the target's periphery that could be "sacrificed" in terms of dose coverage to "save" a proximal risk organ without compromising the tumor control, while underdosing other parts of the target would lead to an insufficient tumor cell kill and local relapse.

2) Good understanding of the radiation sensitivity of the relevant risk organ, both in terms of maximal point dose as well as tolerable dose load to the specific volumes of the organ.

3) Reliable methodology of target and risk organ imaging, and delineation. This applies to the selection of an appropriate imaging modality, but also to relevant anatomical understanding of the structures.

4) Understanding how well prescribed dose corresponds to the delivered dose. This requires knowledge of the individual organ movements during the treatment and other geometrical uncertainties incl. the differences in the patient positioning on the treatment table.

1.3. Means of dose prescription and reporting

An SBRT target consists of a clinical target volume (CTV), which comprises all visible tumor mass (in Stockholm, Clinical Target Volume is traditionally identical to the Gross Target Volume, GTV). A margin of 5-10 mm in transversal plane and 10 mm in longitude plane is added to confirm a Planning Target Volume (PTV), see figures 1-2. The radiation dose is prescribed to the periphery of the PTV, with at least 67% isodose line, which means that the actual prescribed dose closer to the tumor border, and even more so centrally in the tumor, is

considerably higher than the prescribed peripheral dose. The typical mean PTV coverage in Stockholm is around 120% of the prescribed dose, and the mean coverage for the CTV is slightly above 140%. A usual fractionation for a small peripheral lung tumor as 15 Gy x 3 (=112.5 Gy BED $\alpha/\beta=10$). With this schedule, a usual PTV will be covered by physical dose of at least 18 Gy per fraction, and the CTV with a dose of at least 22.5 Gy per fraction, yielding a total mean biologically effective dose (BED) of 151.2 Gy for the PTV and 219.38 Gy for the CTV.

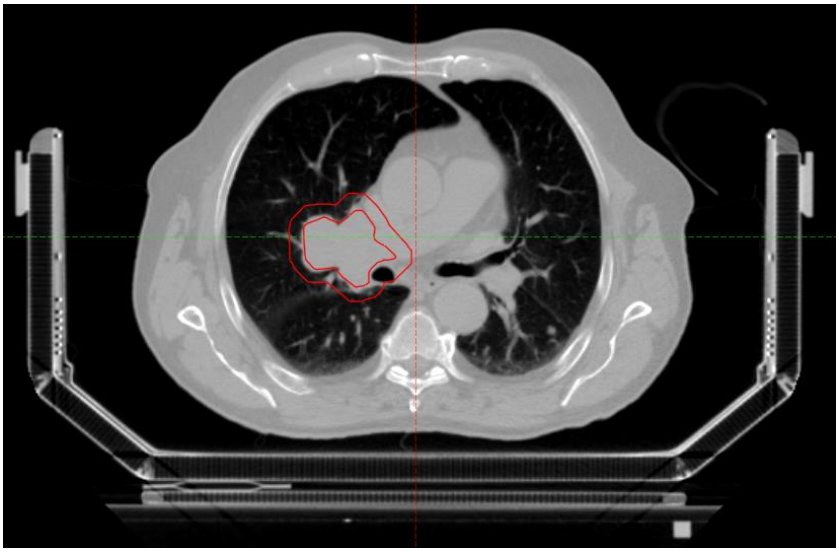

Fig 1. A patient with a large tumor in the right lung hilus, to be treated with SBRT within the HILUS study. CT for dose planning is performed in a stereotactic body frame. The structures of CTV (inner) and PTV (outer) are delineated.

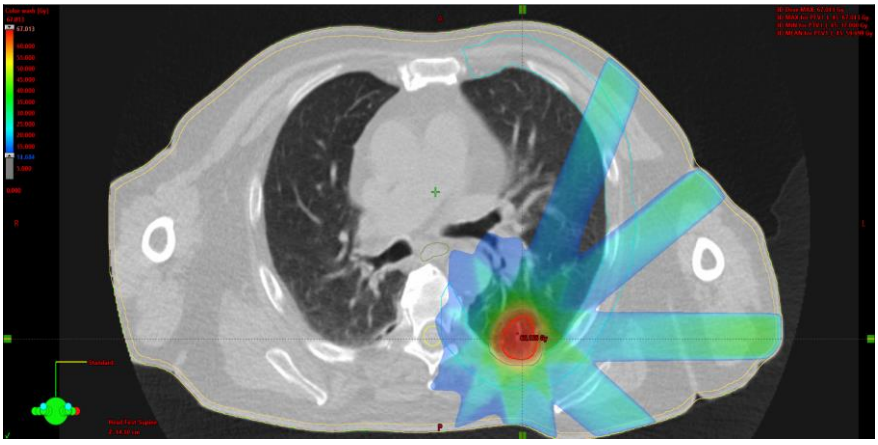

Fig 2. SBRT radiation plan for treatment of a dorsal left-sided lung tumor, the dose levels depicted in colors. Note the rapid dose fall outside of the PTV.

However, how the reported prescribed dose is translated to the planned dose to various components of the target, varies widely between different SBRT centers which in some cases makes the comparison between studies performed by different centers challenging. In some early protocols the prescribed dose refers to the dose in the isocenter of the target (12, 13). Another way of reporting, currently used by most centers internationally, is to specify the percentage to the isodose line (usually 60-90%) covering at least 95% of the PTV (14-17). Furthermore, sometimes there is a requirement of an at least 120% coverage of the entire CTV (17). A fractionation of 60 Gy in 3 fractions, for example, that previously have been frequently used in the Netherlands and North America, has usually been prescribed to 80% isodose line and to 95% of the PTV, presumptively meaning a fraction dose of 24-25 Gy to a substantial part of the target (i.e. CTV), yielding a total BED of 244.8-262.5 Gy.

To perform a meaningful dose-response comparison between different SBRT series, the above-mentioned different means of dose prescription should be reported, in addition to what is currently commonly reported, i.e. fractionation schemes and prescription doses. However, these numbers do not necessarily reflect the whole picture of the target dose coverage and dose delivered to the whole target, neither the existence of "hot" or "cold" spots (i.e. sub-volume of the target with an either high, or too low dose) in the dose plan, both potentially of a paramount importance. In addition to the dose prescription details discussed above, key dose-volumetric parameters for prediction of local control should be determined and homogeneously reported in all SBRT series.

In 2016 Zhao et al analyzed the hitherto largest SBRT single-center cohort of NSCLC with 1200 treated lesions and found that all analyzed dose-volumetric parameters were significantly correlated to local relapse in multivariate analysis (prescribed dose; minimal, maximum and mean PTV doses; coverage doses to 95% and 99% of PTV)(17). For practical reasons authors recommended usage of two key dose parameters: mean dose to the PTV (PTVmean) and dose that covers at least 95% of the PTV (PTV95%). This approach appears intuitive in terms of tumor biology, and could be relatively easy to put into practice. Similar approach has been applied in our study on large tumors (paper II) where two of the key parameters were mean and minimal dose to the GTV, the latter (like PTV95%) mirroring the risk of under-dosing parts of the target. Further research in the field is probably required to

establish a consensus regarding optimal key dose-volumetric parameters for SBRT. A uniform and biologically relevant SBRT dose reporting is inevitable for large database dose-response analyzes, as well as comparison between different SBRT trials and preclinical experiments.

In January 2020, Moreno et al (18) published an analysis of more than 20 000 NSCLC patients treated with SBRT, based on an North American database, analyzing dependence between prescribed dose and overall survival. A weak correlation is found (p=0.032, HR = 1.046, 95% CI: 1.004 – 1.090) between a prescribed BED below 130 Gy and worse survival; however, means of prescription were not specified and may have varied between 60-90% to isodose line over time and between the participating centers (16, 17, 19), which means a significant dose variation to the target not accounted for in the analyzes. Furthermore, while only analyzing correlation between dose and OS, the authors compare their own suggested dose threshold of 130 Gy BED to the thresholds established in two other dose-response studies (17, 20), where 130 and 125 Gy BED were predictive for improved local control. However, the numbers in the latter reports regard the mean dose to the PTV, which is not the same parameter as prescribed dose, used by Moreno and colleagues. As shown in the Stockholm experience based calculation example above, the mean BED to PTV and the prescribed BED may differ more than 30%. This kind of confusion between different ways of referring the radiation dose is still very common in SBRT studies and demonstrates significant room for improvement in terms of uniform and biologically relevant dose reporting.

1.4. Indications for SBRT

Primary NSCLC. As mentioned earlier, SBRT showed excellent rates of local control for primary NSLCL, between 90% and 98% in different series, which made it an established treatment option for inoperable non-small cell lung cancer (3, 7). However, for operable or border-line operable patients, the use of SBRT is controversial (8, 21, 22). Comparison between surgical and SBRT series usually shows superior survival for NSCLC patients undergoing surgery, however, this may be partly explained by the selection bias, as the inoperable patients are older and usually have underlying medical conditions. In an early Japanese study, 64 medically operable patients who refused surgery and were treated with

SBRT, had local tumor control and survival comparable to surgical series (23). Two randomized phase 3 studies were started, aimed to perform head-to-head comparison between SBRT and surgery, but both were shut down due to poor accrual. Interestingly, pooled analysis of patients in both studies showed significantly improved local control and survival after SBRT compared to surgery (24). However, the analysis received criticism, partly due to the low number of patients in the cohort, and partly because the outcome in the surgical arm was worse than in comparable surgical data. Currently, there are three new ongoing prospective trials for primary lung cancer, with randomization between SBRT and surgery (22).

Oligometastatic disease. The concept of oligometastatic disease, as a biological intermediate state between localized and widely spread cancer, has existed for more than three decades (25). It predicts that there are patients with metastatic cancer, where cure or at least prolonged survival can be achieved with local ablation treatment. Usually the oligometastatic disease is defined as at five metastases or less, found in no more than two different organs. The existing preclinical evidence for the concept has long been only indirectly supported by multiple single-arm studies, where patients with metastatic cancer of various origins showed better survival than expected when treated locally, for example with SBRT (26). However, during recent years several prospective randomized trials showed both superior progression free survival (PFS) and overall survival (OS) for oligometastatic patients who received local ablative treatments, compared to those who received standard treatment (27-30).

1.5. Local control evaluation and normal post-irradiation process

In Sweden, radiological follow-up post SBRT consists of a CT every 3 months during the first two years, and thereafter every half a year up to five years' post-treatment. FDG-PET/CT is not performed routinely for treatment evaluation. During follow-up, nearly all patients develop inflammatory changes of the lung parenchyma corresponding to the high radiation dose region (31-33), that subsequently undergo fibrotization and shrinkage, mostly in cranio-caudal dimension, see figures 3-7.

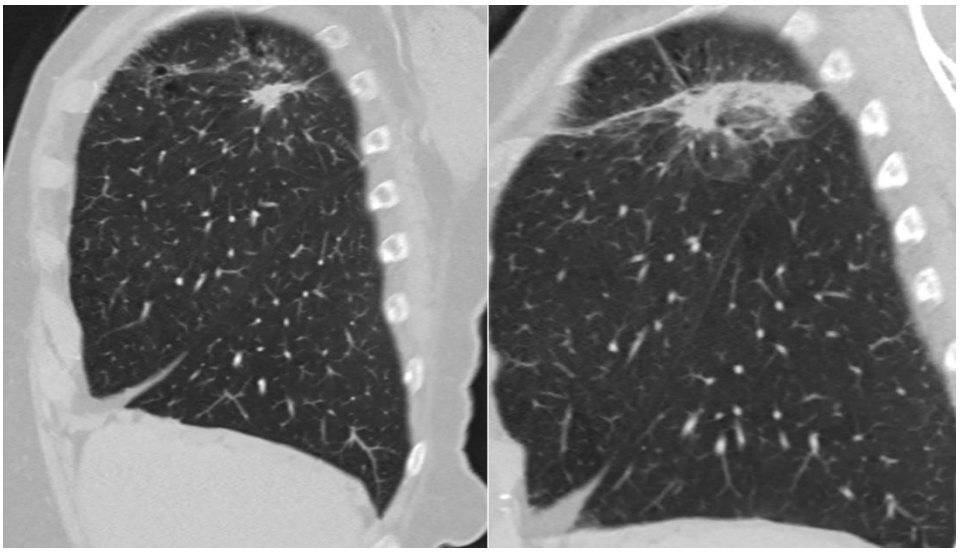

Fig 3. Normal 3 and 9 months post-SBRT dynamics on sagittal lung images. Despite enlargement of the post-radiotherapy fibrotic opacity, there is no suspicion of local progression, and no investigation with PET/CT is required.

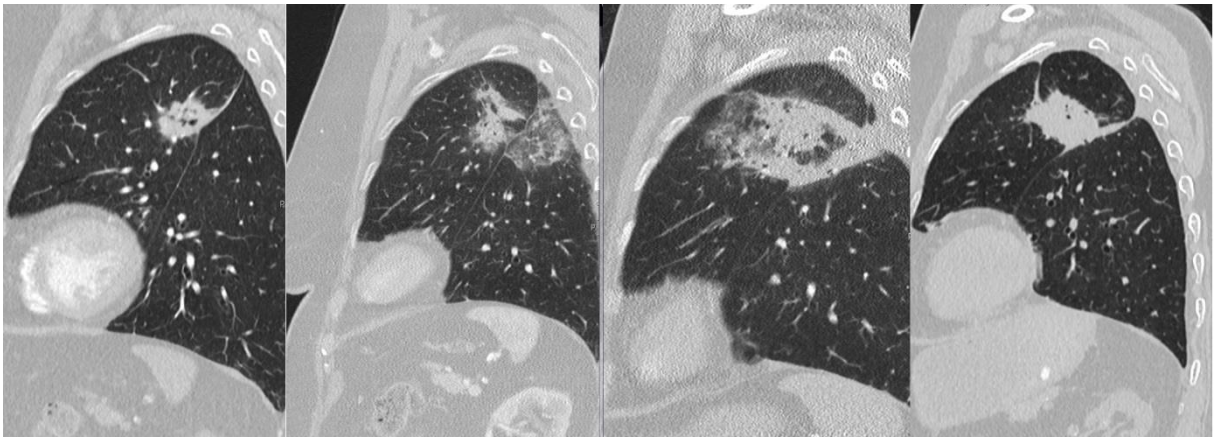

Fig 4. Normal dynamics from pre-SBRT on the left, to 3, 6 and 9 months post-SBRT respectively to the right. Note the initial inflammatory changes around the target, the formation of a fibrotic circle and thereafter final fibrotization.

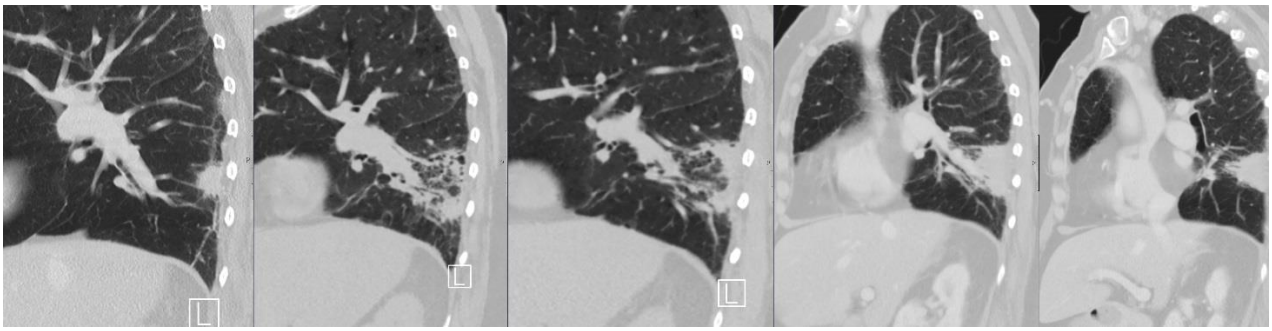

Fig 5. Normal dynamics, from pre-SBRT on the left to 6, 9, 12 and 15 months after SBRT of a dorsal subpleural lung tumor, on sagittal images. Note that the final fibrotic lump is substantially bigger than the original tumor. RECIST criteria for SBRT evaluation should only be applied with knowledge of the method's ablative nature. Here, there is no suspicion of local progression on any of images. Nor does any of the findings requires further investigation with PET/CT.

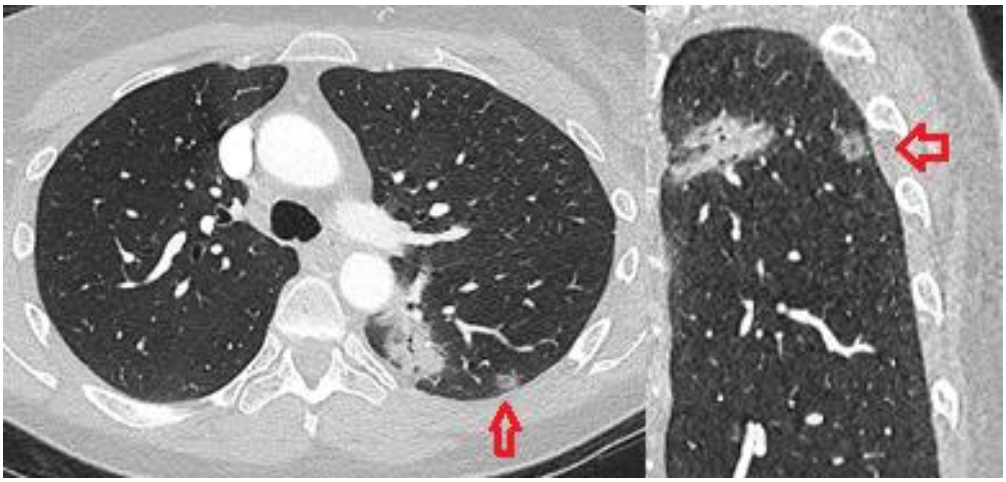

Fig 6. Three-month follow-up after SBRT of a small metastasis from pancreatic adenocarcinoma medially in the left lower lung lobe. The picture represents normal inflammatory reaction corresponding to the high dose area. Notice a small inflammatory opacity (red arrows), at the edge of the high dose area, incorrectly described as a new metastasis.

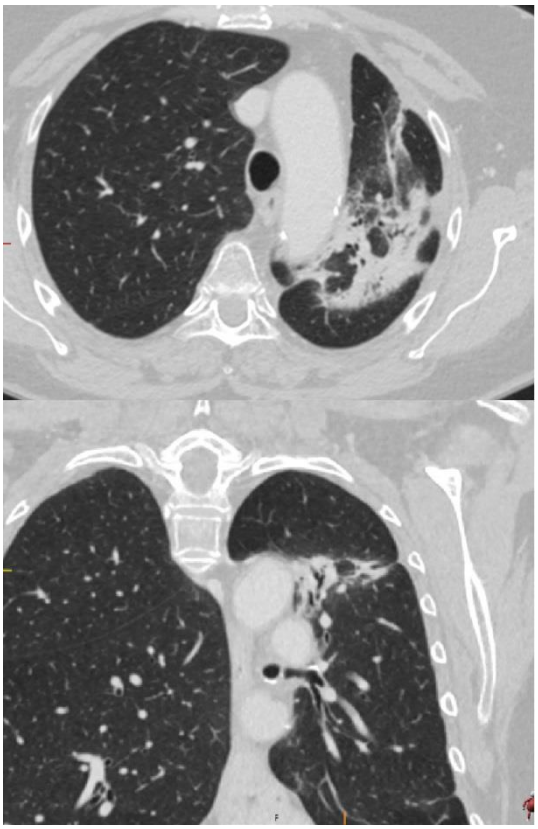

Fig 7. *Normal findings 3 months post-SBRT of an apical left sided lung tumor. The opacity contains both ongoing inflammation and elements of advanced fibrotization. Notice the large spread of the opacity on the axial image, and very limited size in cranio-caudal dimension on coronal image. In size and form, the opacity reminds of the high-dose area on the radiotherapy plan.*

In the early era of SBRT these normal changes created uncertainties regarding response evaluation and arouse (false) suspicion of local progression. For instance, Timmerman et al in a report from 2006 describes how 17 of 70 patients (24%) showed up with enlargement of the target, or other abnormalities on three-month follow-up CT post-SBRT, requiring a PET or a biopsy (whereof all were negative) (16). This diagnostic challenge has been nearly completely overcome since the normal course of post-SBRT lung changes has been studied more closely.

From a pure ground glass-consolidation corresponding to a high dose area, indicating an ongoing inflammatory process, the post-SBRT opacity enters a process of shrinkage in craniocaudal direction and develops a tiny fibrotic rim, indicating the beginning fibrotization. Centrally in this oval or circular fibrotic frame, the dense post-radiation tumor rest is usually visible. Subsequently the consolidation shrinks and undergoes further fibrotization, where the above-mentioned fibrotic circle/oval fuses with the tumor rest, sometimes forming a fibrotic lump that is substantially bigger than the original tumor. This fibrotic lump does not in itself indicate local tumor progression. In most cases, it will further shrink in cranio-caudal dimension, though rarely, predominantly in cases with an originally large-sized target, it may remain unchanged over several years. The best way of distinguishing between a voluminous

fibrotic rest and a local tumor recurrence is by evaluating the dynamics of the process (33). In our institutional experience, cases that show normal temporal pattern in the treated area, do not require PET/CT or biopsy. In a rare case of local recurrence, the latter usually appears as a separate slowly growing tumorous structure at the edge of the fibrotic scar.

In cases when the high dose area is located near a firm structure, such as thoracic wall or mediastinum, where the shrinkage of the nearby-located tissue may proceed differently, the post-SBRT image evaluation may be challenging. SBRT of centrally located lung tumors may lead to a formation of atelectasis which may embed the post-SBRT fibrotic scar tissue and make it difficult to follow radiologically. Furthermore, adjacent to a solid structure, a post-SBRT scar tissue may rotate in space and take new forms on the axial CT projection. This underlines the importance of evaluating the post-SBRT images in at least three dimensions. In case of uncertainty, a sooner control with CT, FDG-PET/CT (34) or a biopsy may be considered.

The normal post-irradiation process may accelerate in cases involving a large target, location near a large bronchus, high irradiation dose, healthy lung (i.e. without emphysema) and even more so in presence of interstitial lung disease. In cases of irradiation of large bronchi, the course of the radiation induced inflammation may be significantly prolonged. Also, certain forms of systemic cancer treatment, such as immunotherapy, or more rarely tyrosine kinase inhibitors (TKI) may act as pro-inflammatory agents, and thus increase or reactivate radiation related inflammatory changes. On the contrary, the expected inflammatory process post high-dose radiation is less prominent and slower in cases with a small target, low irradiation dose, peripheral tumor location and emphysematically transformed lung. Other details of the normal process are well known and describes elsewhere (33).

1.6. SBRT and the RECIST criteria

The RECIST criteria, which are widely used in oncology for objective measurement of response should generally not be used for evaluation of local treatments (35). However, since it has historically been used in SBRT series, it must be emphasized that RECIST criteria

cannot be directly applied for the follow-up after SBRT without understanding of the underlying biology (36-38).

First, one needs to remember the ablative and definitive nature of the treatment, which is comparable to surgery. The high radiation dose delivered in most SBRT treatments, as well as the excellent LC-rates demonstrated by the studies, suggest that total eradication of all tumor cells within the target needs to be assumed until proven otherwise (see the case presented in figure 8). Subsequently, even though the treated lesion rarely disappears completely on the follow-up CT, the RECIST response evaluation should be CR (complete response) and not PR (partial response) or SD (stable disease) – with only a few exceptions, such as cases where the target has been significantly under-dosed, incorrectly delineated, or potentially missed during treatment. In patients that are followed radiologically after cancer surgery, there often exist consolidating fibrotic or atelectatic tissues around surgical clips and threads – which in sense of RECIST-assisted radiological follow up may be regarded as equivalent to normal post-SBRT inflammation. Like normal post-op changes, post-SBRT inflammation and fibrosis should not be measured according to RECIST, unless it shows signs of local tumor progression discussed above.

Second, the final fibrotic scar, whether flat or round in shape, or whether being smaller or larger than the initial tumor, should not be subjected to RECIST-measurement, as this would lead to incorrect biological conclusion that the tumor is not completely eradicated. The only way to differentiate between viable tumor and fibrosis on CT, is by evaluating if the hitherto dynamics is following an expected pattern (see previous chapter), or deviates from it.

The RECIST criteria at follow-up after SBRT can mainly be used at two clinical scenarios:

a) Suspicion of new lesions that appears at the edge of the fibrotic post-radiotherapy scar. They may appear either as bulky changes, or as characteristic circular contrast enhancement charges (fig 9-10).
b) Growth of the stabilized, chronic fibrotic scar or lump, which has been formed after the current inflammatory changes are fully healed. Usually this growth occurs in

caudo-cranial dimension (33, 37). The tumor-suspected growth of the lesion may be assessed according to RECIST (35).

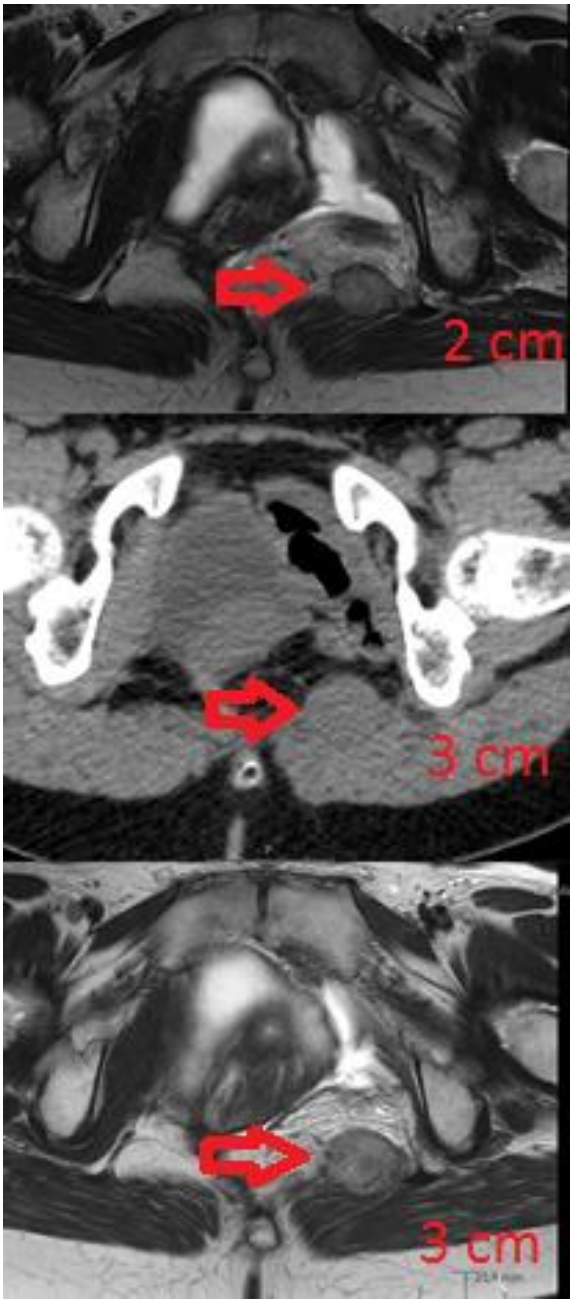

Fig 8. Pelvic tumor treated with SBRT, here presented with an MRI 3 months before, and an MRI 3 months after, radiotherapy. Progression from 2 to 3 cm occurred between the first MRI and the SBRT. Without taking the treatments' ablative character into account, the radiological evaluation was performed between the two consecutive MRIs, with an incorrect conclusion of local progression after SBRT. The patient was operated, without finding of any malignant cells.

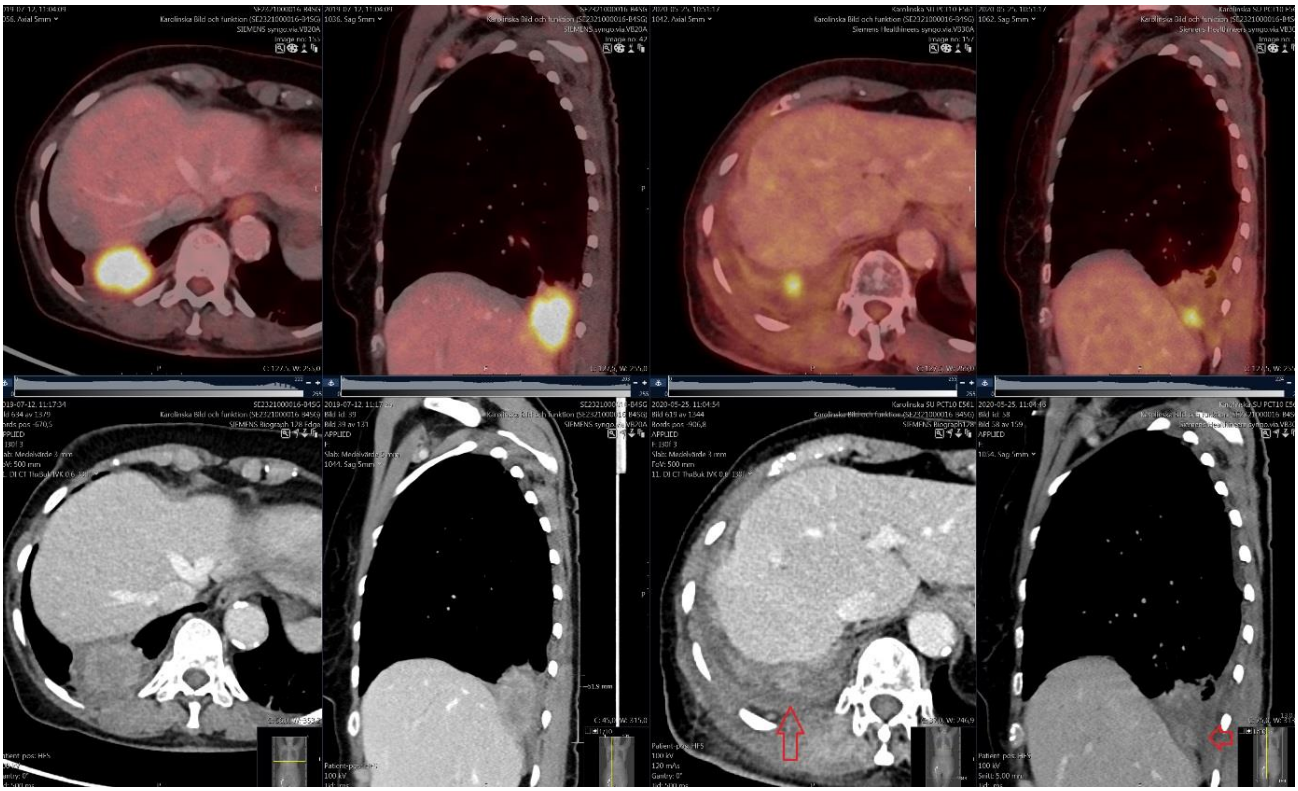

Fig 9. Before and nine months after SBRT of a large dorsal right-sided lung tumor. A local recurrence occurred in the periphery of the target nine months post-SBRT and was confirmed by a PET/CT and a biopsy. Note the circular contrast enhancement (red arrows), which is a strong radiological sign of malignancy.

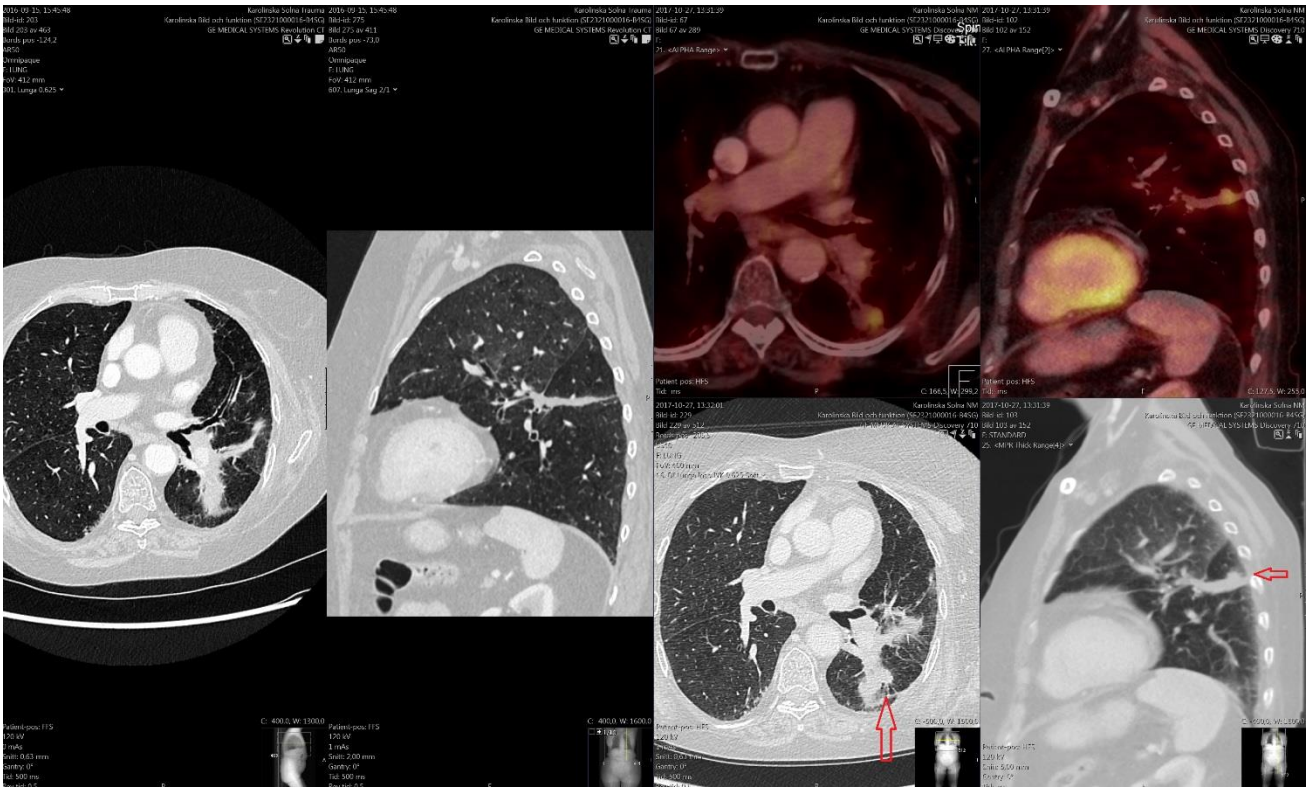

Fig 10. An unusual case of local relapse four years after SBRT of a dorsal left-sided lung tumor, to the left before, and to the right after, the development of a local recurrence with a weak FDG-uptake on PET/CT. Note the emergence of a small bulky change (red arrows) between the left and the right CT images. The process falls within what can be measured and evaluated with RECIST.

1.7. Toxicity

Toxicity is graded according to the Common Terminology Criteria for Adverse Events (CTCAE), where the side effects of the treatment are graded as mild, causing no symptoms (grade 1) to fatal (grade 5). Grade 2 is defined as the symptoms that require no treatment, Grade 3 – require treatment but not inpatient care, and Grade 4 – require hospitalization and are potentially life threatening.

As mentioned earlier, a geometrically precise, high-dose radiation treatment with very high dose to the target and rapid fall-off in the periphery, both spares large volumes of nearby healthy tissue and distantly located sensitive organs, but involves substantial risks to proximally located sensitive organs. The toxicity from SBRT depends on the patient's

individual radiation sensitivity, which organs are at risk of being exposed to high irradiation dose, the maximum radiation dose received by the organs at risk, and more specifically the volumes of the risk organ tissues that receives a certain level of radiation dose (39-51). The risk organs can be simply divided into parallel and serial, where the parallel ones consist of multiple units that function relatively independently, while serial organs constitute chains of interconnected units where the whole organ can lose its functionality if only a small part is damaged (52). Typical parallel organs are liver and lungs, while examples of serial organs are bronchi, bowels and nervous structures. Below follow brief descriptions of the most important risk organs within the SBRT field.

Central bronchi, or proximal bronchial tree (PBT) consists of trachea, left and right main bronchi; on the right side the upper lobar bronchus, the intermediate bronchus, the lower lobar bronchus as well as the middle lobar bronchus; on the left side, the upper lobar bronchus, the lower lobar bronchus, and the lingual bronchus.

In 2006 Timmerman et al showed increased mortality in patients with tumors near central airways that were treated with the same dosage and fractionation as patients with peripheral lung tumors, which was later confirmed by other series (16, 39, 40, 53-67). The two main lethal side effects from central airways post-SBRT appear to be radiation pneumonitis (RP) and bronchial hemorrhage. Since the airways is a serial organ, it is important to find out the maximum tolerable point dose as well as the dose limits for small volumes of the separate parts of the bronchial tree, to be able to treat patients with SBRT in a safe way.

In the above referred study by Timmermann, the definition of central tumor location was within 2 cm from any part of the PBT. A category of an “ultra-central” location has later emerged to describe the particularly high-risk tumors locations, a term that in different series included locations from within 1 cm from different parts of the PBT to abutting or invading the PBT, esophagus, pericardium, lung veins etc. (55, 56, 58, 64, 68-70). In the context of bronchial toxicity, the term “ultra-central” has in Stockholm been used for tumors within 1 cm from the any part of the PBT (involving the distal 2 cm of trachea as well as main and lobar bronchi) as in the prospective HILUS study (71). A specific high-risk group of patients with tumors within 1 cm from trachea and main bronchi was further defined (corresponding to group A of the HILUS study). The intermediate bronchus was not seen as a part of the main

bronchi due to the traditional bronchial nomenclature (72), although there are varying opinions whether it should or should not be included in the primary bronchial tree (73-76).

Studies on radiographically visible bronchial toxicity show that a higher maximum radiation dose is required to achieve a total occlusion of a main or intermediate bronchus, compared to a lobar bronchus (66, 67). However, no correlation between clinical and radiological toxicity was seen. Since total fibrotization of an irradiated lung volume, including total collapse of small bronchi located therein, being imbedded in the local fibrotic scar, is a sign of a completion of a normal post-irradiation inflammatory process (32-34), one may reason whether the "high-grade radiological toxicity" of small bronchi is rather consistent with a positive clinical outcome, where potentially harmful chronic inflammation has successfully healed. Contrary, the sub-total bronchial damage which more often occurs in larger bronchi (67) may lead to a long-term inflammation with subsequent weakening of the barriers between luminous organs (77, 78), such as bronchi and vessels, potentially increasing the risk of intrabronchial bleeding.

Lung parenchyma, is an important parallel organ that is exposed to radiation in nearly all cases of SBRT of thoracic tumors. Some degree of inflammatory response in the high-dose area is a part of the normal post-SBRT dynamics (see separate chapter above), while symptomatic radiation pneumonitis (RP) is the most common side effect after SBRT and varies between 9 and 28% in different series, and can be mild to fatal (39, 79-81). The tendency to symptomatic RP is amplified by several factors including central location of the target and subsequent SBRT related bronchial damage, large lung volume irradiated, interstitial lung disease (ILD) as well as some systemic anti-cancer agents such as PD1/PDL1-inhibitors or to a lesser degree tyrosine kinase inhibitors (TKI) (39, 79). Most likely, all factors that induce inflammation in the lung parenchyma also amplify the tendency for RP, including lung infection. During the past year, we have found at least two cases at our institution, where RP suggestively was aggravated by the Covid-19 infection. At radiological follow-up, it is not uncommon that RP is confused with progressive disease or bacterial infection, which can significantly impair the patient's care, as RP needs to be treated with corticosteroids. Some clinical RP cases are presented in figures 11-16.

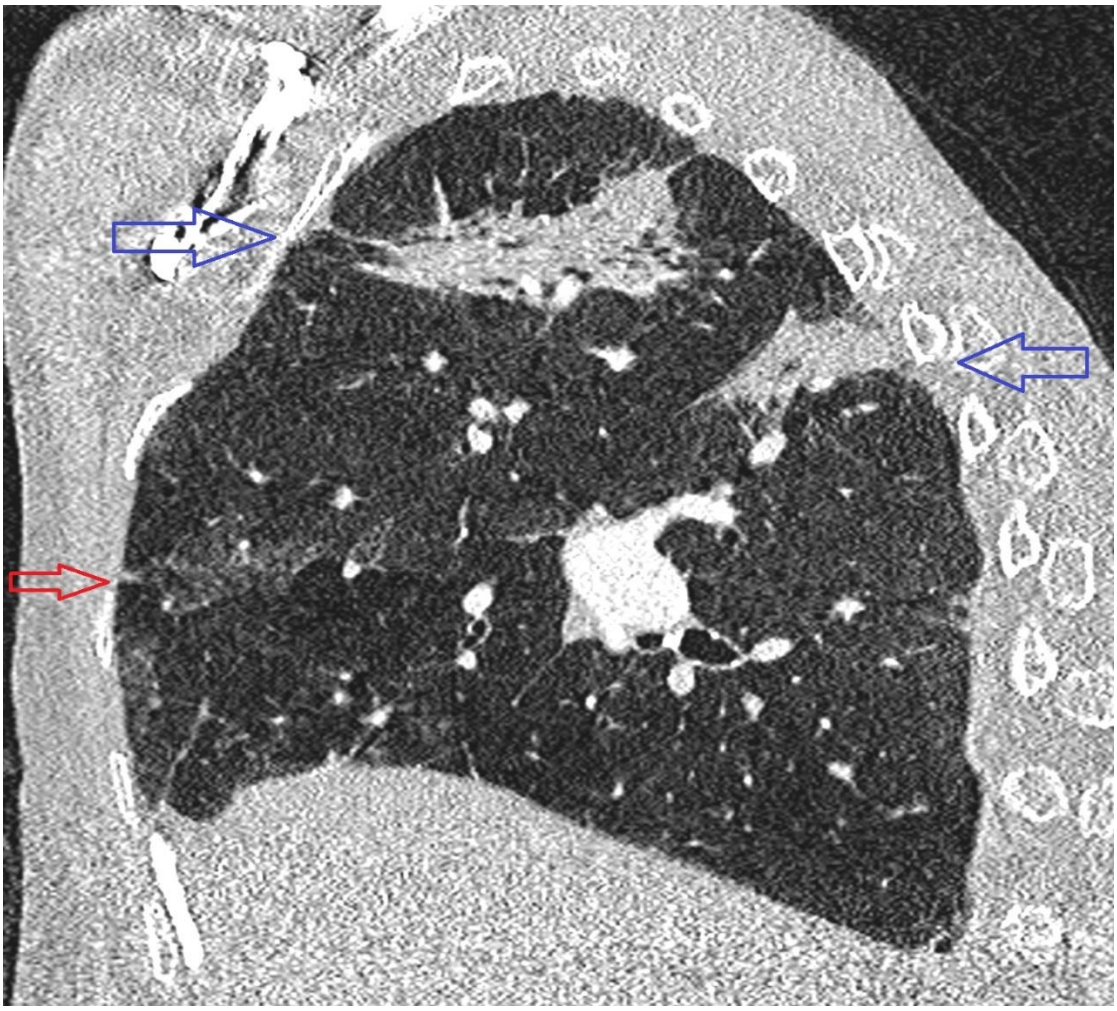

Fig 11. 90 year old woman, 3 months post SBRT of a large apical lung tumor, sagittal view. Note large fibrotic opacity corresponding to high radiation dose area (blue arrows). The consolidations in upper and lower lobe seem to be at different levels, which is due to different shrinkage potential in apical parts of the two lobes – the consolidations "separated" during the shrinkage process. There is no suspicion of local recurrence or metastases, and no further examination is warranted. The large and dense fibrotic reaction does not itself raise any suspicions of symptomatic radiation pneumonitis. However, the thin inflammatory opacity far from the high-dose area (red arrow) is strongly suggestive of "out of order lung inflammation", thus symptomatic RP.

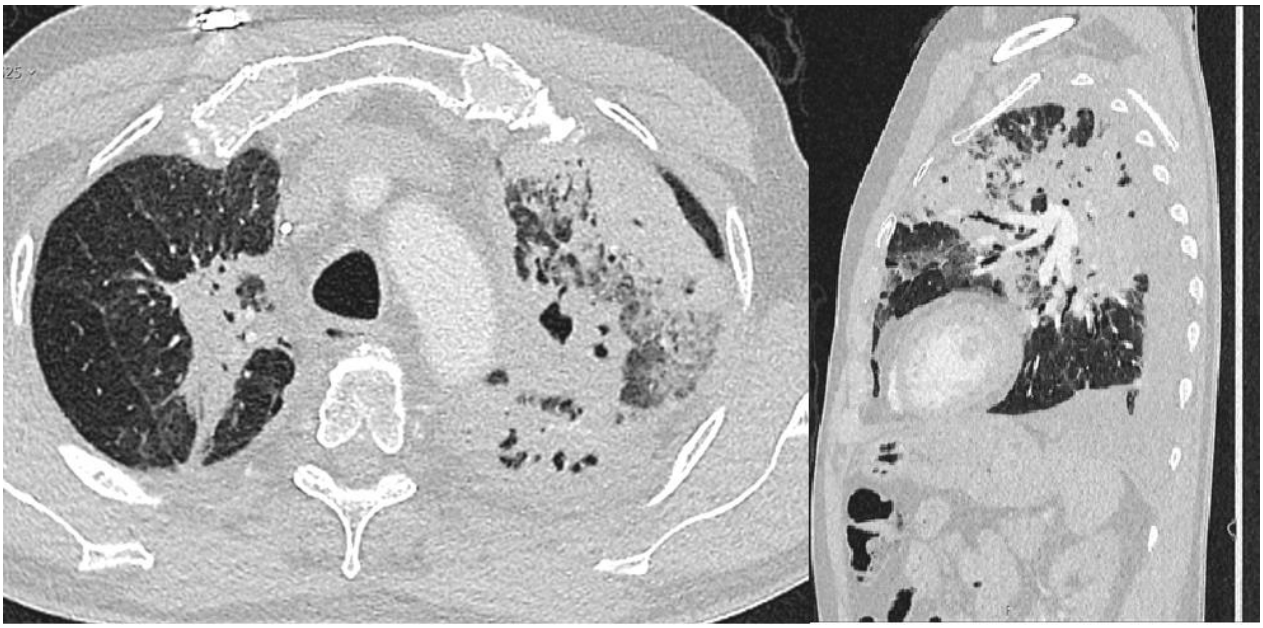

Fig 12. Highly pronounced bilateral RP after palliative irradiation 5gy x 4 of a left-sided lung tumor and subsequent immunotherapy, more intense than expected after this type of radiotherapy alone. The local lung inflammation (RP) is here clearly enhanced by the systemic inflammation induced by the immunotherapy.

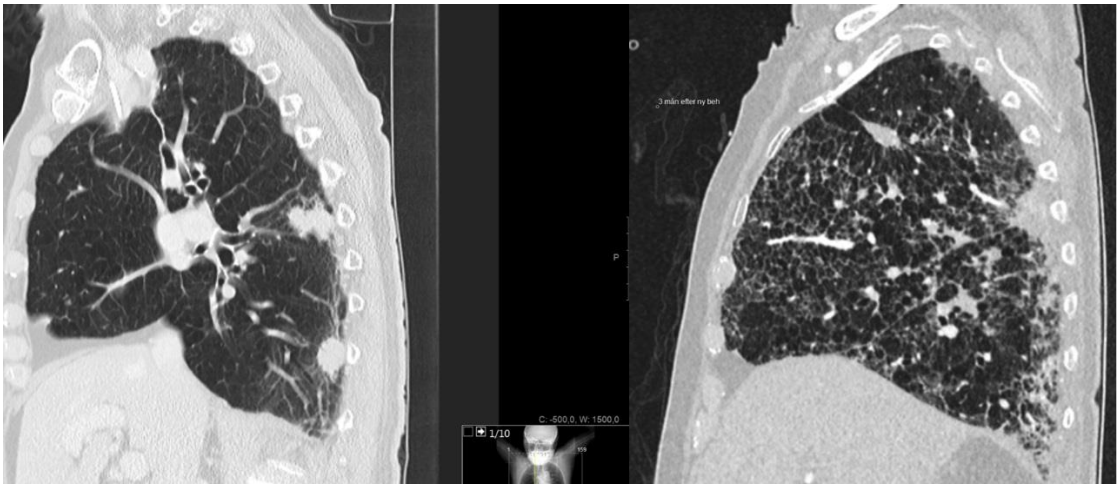

Fig 13. Symptomatic mild RP three months post-SBRT of two dorsal right-sided lung tumors (image to the left – before SBRT, image to the right – three months after SBRT). Note the general pattern of thin opacity spread throughout the whole lung. Signs of inflammation outside the SBRT high-dose area is a main radiological sign of symptomatic RP.

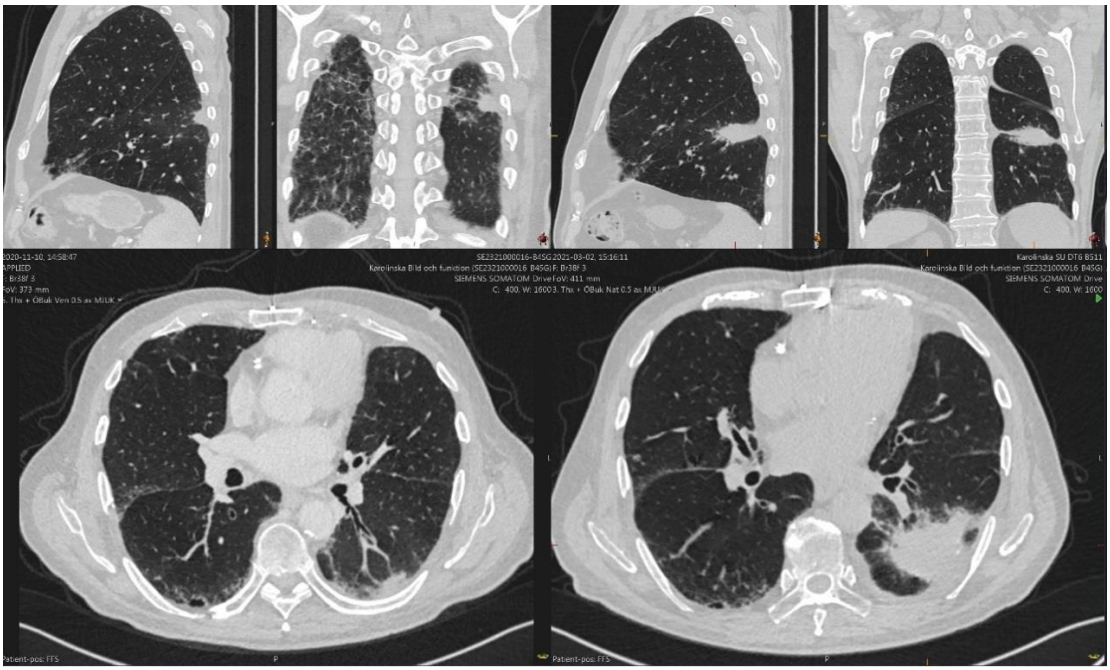

Fig 14. Four (to the left) and seven (to the right) months after SBRT of a dorsal left-sided lung tumor. The local reaction that appears after seven months is unusually large, with an unusually rapid course, but remains within the SBRT high-dose field. There is no radiological suspicion of "out of ordinary" radiation pneumonitis. Nor does the status give rise to any suspicion of local tumor progression.

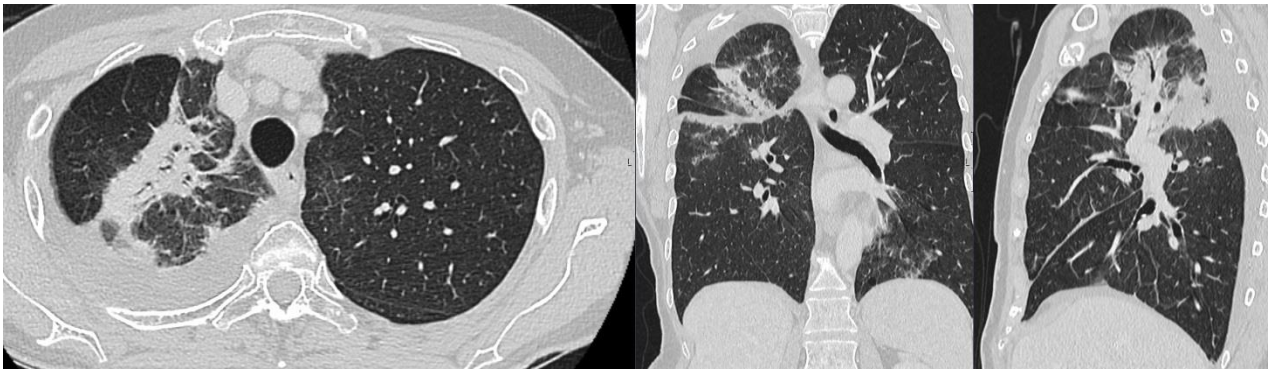

Fig 15. Six months after an SBRT consolidation of a primary EGFR-mutated lung cancer, that showed radiological signs of local resistance against the tyrosine kinase inhibitor (TKI) Tagrisso. The patient was treated with Tagrisso both before and after SBRT. Note the pronounced RP with secondary pleural effusion, where the two inflammation driving treatments probably reinforced each other's lung toxicity.

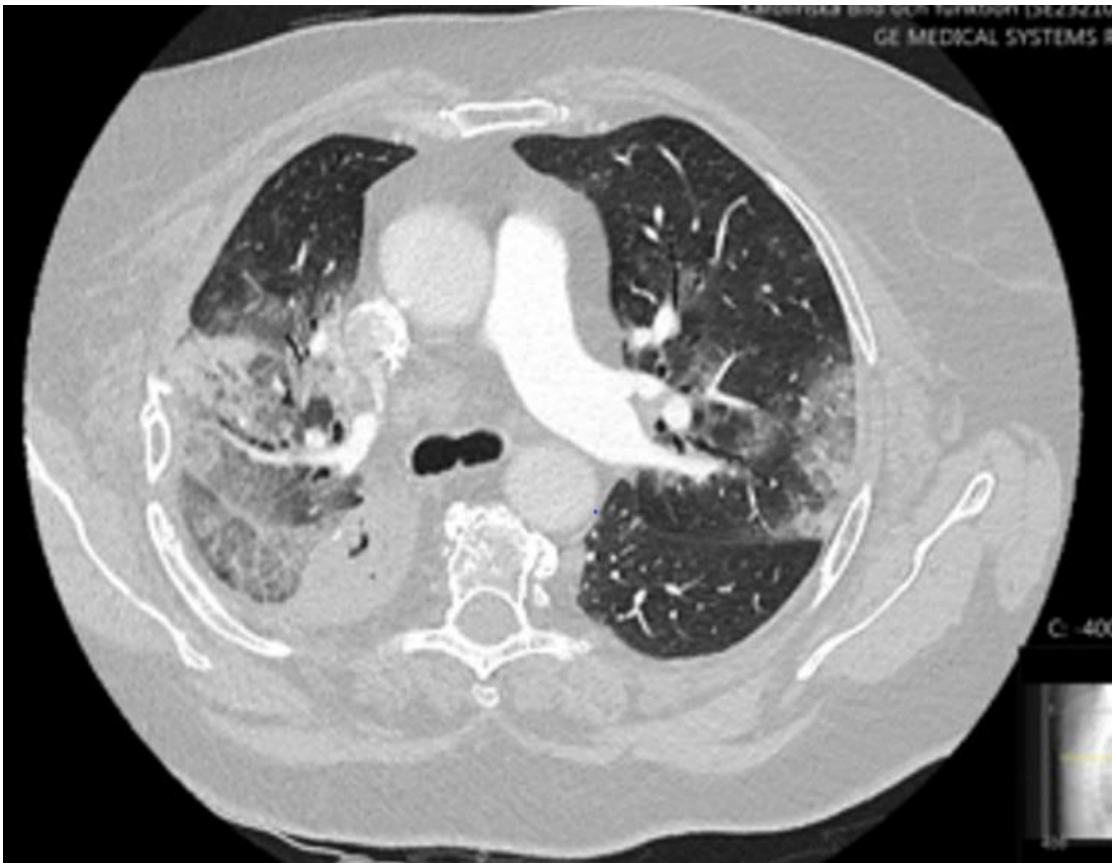

Fig 16. Patient with a right-sided lung cancer, under treatment with conventional radiotherapy, who had received only 36 of 68 Gy before developing a symptomatic Covid-19 infection. The image demonstrates bilateral inflammatory changes consistent with the Covid-19 pneumonia, on the right side also geometrically corresponding to the radiotherapy high-dose area, however significantly more pronounced than expected after only 36Gy. The image suggests synergy between the two inflammatory processes.

Esophagus is another serial organ that restricts SBRT to centrally located thoracic tumors. The reported toxicity includes esophagitis, stricture, rupture and esophago-tracheal fistula. Unlike the central airways, the radiation sensitivity of the esophagus is relatively well studied, and clear dose-volume dose constraints exist (40).

Heart, in terms of radiotherapy, is a mixed organ consisting of both parallel (muscles) and serials (vessels, valves) structures. Cardiac complications from conventional radiotherapy are relatively well studied, with the material coming almost exclusively from long-term survivors from such as young breast cancer and Hodgkin's lymphoma patients. The cardiac dose

constraints are thus mainly known for conventional fractionation regimens, while it is not completely clear what dose-volumes constraints should be applied for different parts of the heart in the SBRT context. The most important radiotherapy related cardiac side effects are ischemic heart disease and heart failure, which are not entirely easy to study in the context of SBRT since they are non-specific and widely spread in the elderly co-morbid SBRT population (40, 82-84).

Peripheral nerve plexuses are serial organs where excessive irradiation may result in symptoms peripherally of the damaged site. The most frequent adverse side effects are numbness, pain and loss of function (40, 85-87). The most common peripheral nerve plexus in the context of SBRT is plexus brachialis, which may be exposed to radiation during treatment of apical lung tumors. To avoid excessive toxicity, the exact dose-volume constraints need to be established, and a robust methodology for organ delineation need to exist in each SBRT center. The plexus brachialis is a tiny, anatomically complex structure, notoriously difficult to delimit on the 3 mm thick slices of the non-contrast enhanced dose-plan CT. However, the parts of the plexus that are closest to the lung apex, being the high-risk sub-volumes in the context of SBRT, are fortunately also that parts of the plexus brachialis that are most visible on CT. In difficult delineation cases, images from earlier performed diagnostic CT images with thin slices and contrast enhancement, or an MRI, can be used. In cases when the tumor is located close to the lung apex, even the dose plan CT needs to be performed with i.v. contrast and thin slices.

Bowel and liver, are two important abdominal risk organs that need to be considered in the treatment of abdominal tumors. The liver is a large parallel organ, which mainly moves along with the respiration. The bowel is a serial organ that moves both along with the breathing cycle and has the physiological motility of its own, where local changes of the caliber and random position switches of bowel loops are seen frequently. Liver has relatively low radiation sensitivity at high doses to small volumes. However high doses to large volumes, especially in patients with impaired liver function (i.e. cirrhosis), may lead to radiation induced liver toxicity (RILD), which is a semi-acute feared complication occurring in the form of rapidly deteriorating liver function. This consideration is particularly relevant since many of the liver targets constitute primarily hepato-cellular carcinoma (HCC), which often occurs because of chronic liver disease (41, 43, 50, 88). Bowel is highly sensitive of high doses to small volumes; radiation overdose may result in pain, perforation, stenosis,

inflammation or bleeding. Dose restrictions for the different parts of the intestine are relatively well described (42, 48, 51). The high motility of the organ constitutes an uncertainty between planned and delivered dose; on the other hand, the movements between fractions has a potential of spreading the total dose to different parts of the bowel, and thus reducing the risk of high punctual dose load.

1.8. Tumor radiobiology of hypo-fractionated radiotherapy

In conventional hyper-fractionated radiotherapy, there are five basic principles of radiobiology – so called the five R's: repair, redistribution, re-oxygenation, repopulation and radiosensitivity. Repair means in short division of the total radiation dose in small fractions where a single fraction often only cause a slight damage to the cell, mostly resulting in a single-strand DNA breach. The ability to repair such a slight damage is better in a healthy cell compared to in a cancer cell, why the healthy tissues may repair all the damages between the treatment fractionations, while the cancer cell accumulates the damages and subsequently dies. Redistribution means that different cells within the tumor are in different stages of the cell cycle, and therefore not equally sensitive to irradiation. The cells in S-phase of the cell cycle are relatively radioresistant, but over the course of radiotherapy they may have left the resistant phase becoming easier to kill by another radiation treatment fraction. The concept of re-oxygenation applies to various degrees of tumor hypoxia that reduces the radiosensitivity of the tumor, since the cell kill in this type of radiotherapy mainly occurs via free oxygen radicals. However, the hypoxia in different tumor sub-volumes varies over time, and a tumor cell that has been hypoxic during one radiation fraction may be well oxygenated during another. Furthermore, when the well oxygenated cells located close to the blood vessels die during radiotherapy, the hypoxic cells can move closer to the vessels and thus become better oxygenated. Repopulation is rapid cell division that occurs as a reaction to cell death during radiotherapy, and may cause incomplete tumor kill when the delivery of the ablative dose is extended over too long time. Radioresistance is the "newest" R of the radiobiology, referring to additional, other than above-mentioned intrinsic factors of treatment resistance due to various biological properties of the cancer cell (89, 90).

The rapid paradigm shift from multiple (up to 30-70) low dose fractions in conventional radiotherapy, to one single high-dose fraction in stereotactic gamma knife radiosurgery, may be regarded as a radical breach with classic radiobiology, whose principles are largely based on hyper-fractionation. Partially, decreased necessity of dividing treatment into many fractions is explained by the stereotactic technology that allows for exact dose delivery to the target, excluding normal tissues from high dose area. On the other hand, one single radiation dose, as in stereotactic gamma knife radiosurgery, would not allow for redistribution of cells along with the cell cycle, nor re-oxygenation of hypoxic cells between the treatment fractions – thus missing the advantage with fractionation predicted by the second and the third principles of classic radiobiology. (However, SBRT with 3-5 fractions would partly allow for redistribution and re-oxygenation compared to one-fraction stereotactic Gamma Knife radiosurgery). Since hypoxic tissue is much less sensitive to ionizing radiation and may require three times the dose compared to well oxygenated tissues to achieve the same cell kill, the hypo-fractionation may in theory have become a significant weakness of stereotactic radiotherapy/radiosurgery, risking insufficient tumor control (91, 92). Despite this, SRS and SBRT demonstrated very high rates of tumor control in all clinical studies, superior to that of conventional radiotherapy (see previous chapters). This apparent contradiction needed an explanation, which was partly given by the concept of "new radiobiology", which briefly consists of two main theories.

a) Endothelial damage and/or collapse of the microvasculature in the tumor leading to tumor necrosis. This theory emphasize that the tumor's blood vessels are more radioresistant to small fractional doses than the cancer cells, and therefore may survive through the multiple low dose fractions of conventional radiotherapy. Important clonogenic cells as well as tumor stem cells may be protected from radiation in so called "perivascular niches". Beginning from 8-10 Gy per fraction, tumor vasculature is being increasingly sensitive for ionizing radiation, which leads to early circulation collapse and tumoricidal effect exceeding ditto predicted by the traditional radiobiology (93-97). Despite some criticism regarding the interpretation of preclinical results (98), the idea of direct vascular effect at high doses-per-fraction is now relatively well established (99).

b) High fractional doses may cause rapid tumor cell disintegration and thus abundance of tumor antigen in surrounding micromilieu. This increases the process of antigen presentation between the dendritic cells and lymphocytes, enhancing the T-cell mediated anti-tumor immune response (97). An ultimate expression of this process is so called abscopal effect, which means out-of-field antitumor effect of radiation treatment without any additional systemic medication. This immune-modulation hypothesis has been confirmed via multiple preclinical experiments, as well as some case reports of abscopal effect – the latter mainly form renal cell carcinoma and NSCLC (98, 100). At our institution, there has been at least one case of abscopal effect in an SBRT patient treated for metastatic sarcoma (only one lesion treated). The effectiveness of combination between SBRT and systemic immune-modulation has also been confirmed in a recent phase II study on NSCLC (101), and several phase-3 studies are underway (102). However, the question remains to what extent this immune-modulating effect is unique for modern SBRT/SRS among other radiotherapy regimes, as well as among other ablative local cancer treatments. On the other hand, it is also unclear if there is a need of the immunological mechanism to explain the excellent local response of SBRT, in addition to the explanatory models of the traditional radiobiology. Some preclinical data indicate that optimal dose per fraction for stimulating the immunological response is lower than actual doses in ablative hypo-fractionated radiotherapy, and is around 8 Gy per fractions instead of 15-23 Gy given in most SBRT cases (98). Furthermore, the best proof-of-concept for combination of radiotherapy and systemic immunotherapy to date for NSCLC comes from the PACIFIC trial, involving only conventional, low-dose-per-fraction radiotherapy (103).

While "the new radiobiology" has it obvious place in research on SBRT, some authors have pointed out that high BED per se, which is now possible to deliver thanks to the stereotactic technology, compared to the doses given in conventional radiotherapy, is sufficient to explain the high rates of local control in SBRT/SRS (98). As shown in the calculation examples in chapters 1.1 and 1.3, the total BED of a standard hyper-fractionated radiotherapy in NSCLC in Stockholm is 81.6 Gy. This could be compared to a standard SBRT fractionation in NSCLC, with a mean BED to PTV of 151.2 Gy and mean BED to CTV of 219.38 Gy, which is almost a double and triple radiation dose respectively. One can reason about radiobiology

of a moderately hypoxic tumor, where the conventional, hyper-fractionated radiotherapy "handles" the tumor hypoxia by letting the hypoxic cells gain oxygen between the 34-35 treatment fractions. In the case of a three-fraction SBRT there is some remaining possibility for tissue re-oxygenation, while the cells that remain hypoxic receive an almost triple radiation dose compared to standard radiotherapy. As shown previously in preclinical models, hypoxic tumor tissues may require just a 3-fold dose increase to achieve comparable cell kill as non-hypoxic tumor tissues (92).

One can assume that for some heavily hypoxic tumors (prone to hypoxia due to size, growth rate, histology or other biological properties) the standard SBRT dose-to-CTV (just below 3-fold compared to conventional radiotherapy) may not be sufficient to compensate for hypoxia, resulting in the increased rate of local recurrence. These tumors may need an additional systemic treatment, increased general radiation dose or individualized SBRT plan with a boost to strongly hypoxic areas. Furthermore, in some tumors hypoxic areas may be located in the periphery of the target, and due to technical uncertainties and/or target movement remain outside of the highest dose area. They thus will receive the dose sufficient to control normoxic, but not hypoxic tumor tissue. On the other hand, some tumors with less hypoxic load may be overtreated with the current fractionation and treatment delivery schemes.

1.9. SBRT and risk of local recurrence

SBRT has provided very high rate of local control for tumors of varying sizes and types; however, only few series, generally involving small targets, report a local control of 100% (3). Several factors (except insufficient radiation dose, discussed above) have been addressed as possible predictors for local recurrence, such as tumor size, histology, radiation dose, tumor hypoxia as well as other biological properties.

Everything else alike, large tumor size is a sign of far progressed disease and poor prognosis, which is mirrored in the TNM classification. Large-volume tumors are more difficult to control with ionizing radiation, as they require higher dose, which may depend on amount of clonogenic cells or other biological properties (104). While some early studies of local control in SBRT for NSCLC showed increased tendency for recurrence for T2 tumors compared to

the T1 ditto (4, 5, 8, 105, 106) some centers sought to compensate for large volume (i.e. T2) with dose increase (16, 107) and subsequently found no difference in local control between T1 and T2. Davis et al analyzed 739 NSCLC T1/T2 tumors treated with SBRT and found no correlation between dose (prescribed BED) and local control for T1 tumors. However, for T2 tumors there was a significant correlation between high prescribed BED and tumor control (108), where prescribed doses of <105, 105-149 and ≥150 Gy BED resulted in local recurrence of 32%, 21% and 8% respectively (p=0.029).

It has been speculated whether pretreatment FDG-uptake (expressed as, for example, SUVmax) could be a biomarker for an increased risk of local recurrence for NSCLC treated with SBRT (3). Given that FDG-PET/CT since many years is a mandatory part of diagnostic workup for lung cancer in most developed countries, the issue seems to be a "low hanging fruit" for large scale retrospective as well as prospective studies. To the best of my knowledge, high FDG-uptake before SBRT has until this date not been demonstrated as an independent factor for local recurrence. Kohutek et al (109) analyze 219 NSCLC lesions treated with SBRT and report a correlation between high FDG-SUVmax and local recurrence in a uni-variate analysis. However, in this study also tumor size is predictive for local recurrence and there is a significant overlap between large tumor size and high FDG-uptake. No multi-variate analyzes has been performed in the study because of small sample size (i.e. too few local recurrences). Other series investigating the role of FDG-uptake in prediction of local failure post-SBRT have same shortcomings, i.e. small sample sizes and/or poorly defined aims (3, 110, 111). This issue needs further elucidation, although it is telling that no obvious correlation has been found between high FDG-uptake and local recurrence post-SBRT, despite vast potential research material.

Another variable in a tumors radiation sensitivity issue, is histology. Colorectal cancer (CRC) has in multiple series been shown to have an increased radiation resistance compared to NSCLC (112-114), which has been compensated trough dose increase (115, 116). The increased radiation resistance in tumors of this histology has been attributed to a possible generally increased grade of hypoxia (117, 118). Also, tumor size may play some role for local relapse/radiation resistance in CRC (119-121).

The typical fractionation for a small CRC metastasis at our institution is 17 Gy x 3, yielding a BED α/β=10 of 137.7 Gy. With this fractionation, a mean BED to PTV and CTV is 186.1 and 241.3 Gy respectively. Again, this could be viewed in a context of an ablative (at least, given with an ablative intention) dose in conventional, hyper-fractionated radiotherapy for NSCLC of 81.6 Gy BED.

There is increasing evidence that tumor histologies like renal cell carcinoma (122, 123) and prostate cancer (124) may be more sensitive to high-dose-per-fraction radiation treatment, both in comparison with NSCLC/CRC and with themselves treated with low-dose-per-fraction regimens. The increased effect of high doses per fractions could potentially be explained by the "new radiobiology" referred above, involving the effect on tumor blood vessels and the immune system. For prostate cancer (and sometimes even for RCC), there are speculations that the fundamental tumor biology in terms of i.e. interfractional DNA reparation, is more like a healthy tissue than a fast-growing tumor like NSCLC (this property is expressed as a lower α/β-value, which is thought to be around 1.5 for prostate cancer compared to 10 for NSCLC or CRC). For RCC, the treatment fractionation in Stockholm is equal to that of NSCLC, but rates of local control are somewhat higher (123). Also, we demonstrate excellent local control rates for RCC (more than 90%) also for very large target volumes, treated with doses below 100 Gy BED α/β=10 (125). For prostate cancer, fractionations schemes of 7-8 Gy x 5 or 5 Gy x 10 are used, where the total physical dose is lower than the one given for NSCLC or CRC.

In clinical practice, as well as in most reported SBRT series, the rate of local recurrence is low. Based on the reasoning and cited articles above, the observed cases of local relapse could generally be attributed to two factors (apart from failure to deliver the treatment dose);

a) Too low planned dose to the entire tumor or a part thereof, according to the available knowledge about the tumor's biology. The latter may be especially relevant in cases of target location near a risk organ, such as bowel or central bronchus, when the tumor periphery may be deliberately under-dosed to avoid excessive toxicity, such as bleeding, inflammation, perforation or stenosis (16). Situations with necessary

peripheral under-dosing of the target are probably more common at larger tumor size (which is i.a. demonstrated in our study on SBRT of large tumors) (126).

b) Other unexpected biological properties of the tumor, not known at the time of the treatment planning, resulting in a local relapse despite proper target coverage. Intuitively and based on available data discussed above, it would be reasonable to believe that this situation predominantly arises in large tumors (this is indirectly demonstrated by the fact that patient cohorts with T2 NSCLC tumors in some series need higher doses to achieve same rate of local control as T1 tumors).

The key to preventing local recurrences should be sought in deeper understanding of a tumor's biology. The radiation resistant tumors, or tumor sub-volumes, could be handled through specially adapted radiation plans or additional local or systemic therapy. This requires a reliable methodology of investigation of relevant biological properties of the tumor, that in one or another way mediate radiation resistance (127). Since the total rate of local recurrences after SBRT is low, this type of supplementary investigation (i.e. PET/CT scan with a hypoxia tracer) should be performed in cases that involve an increased risk of local recurrence, such as large tumors or tumors close to organs at risk. In other words, individual study of a tumor's radiosensitivity should be a part of the diagnostic workup in all cases where radiation treatment is indicated, but for various reasons looks to be difficult to plan or perform.

The detailed knowledge of the tumor's radiation sensitivity may be important in order to boost the most radioresistant tumors, or tumor sub-volumes, with extra radiation dose (or adapt the treatment plan in other way, such as increasing the number of fractions, use of radio sensitizers or combined treatment with other antitumoral drugs). Likewise, defining tumors, or tumor sub-volumes, that are extra sensitive to radiation, may allow for a dose reduction necessary to spare organs at risk in the proximity of the target, without risking a local recurrence.

2. Aims of the thesis

The main purpose of this thesis is to identify groups of tumors that are difficult to treat with SBRT, due to size or proximity to risk organs, and to establish approaches for optimal patient selection and the design of the treatment. More specifically, the aim of each paper is described below:

Paper I aimed to investigate radiation toxicity to the brachial plexus, in patients treated with SBRT for a lung tumor in the proximity of the plexus, and to establish the relationship between the toxicity and the dose-volume parameters regarding the radiation load on the plexus.

Paper II aimed to review local control and toxicity in patients with tumors larger than 70 cc, treated curatively with SBRT. Regarding local control, several predictive factors needed to be evaluated, such as minimal, mean and maximal dose to the target, but also tumor size and tumor histology. Toxicity needed to be evaluated considering tumor location in relation to risk organs.

Paper III aimed to prospectively evaluate a risk adapted SBRT protocol for treatment of tumors within 1 cm from proximal bronchial tree (PBT) regarding local control and toxicity, as well as to compare the outcome between group A (tumors within 1 cm from distal trachea or main bronchi) and group B (tumors within 1 cm from lobar bronchi). Additional aim for a retrospective review of the prospectively collected material, was to establish relationship between grade 5 toxicity and several dose-volume parameters to predefined parts of the PBT.

In *Paper IV*, patients with tumors within 2 cm from the PBT, treated with SBRT according to the same protocol as in Paper III but not included in the prospective study, were added to the prospective cohort to broaden the base for the statistical analysis. The first aim was to test the hypothesis generated in Study III, regarding treatment safety for the patients with tumors located more than 1 cm from trachea and main bronchi. The second aims were local control and survival.

3. Patients, materials and methods

3.1. Patient cohorts and study design

Paper I was a retrospective single institutional study of patients treated with SBRT between 2008 and 2013. Around 1000 patients were reviewed manually, and all patients with lung tumors where the epicenter was located above the aortic arch, could be included in the study. All patients with clinical follow-up of less than 6 months were excluded. Finally, 52 patients with 56 tumors, and 55 brachial plexuses-at-risk, were included in the study. Median follow-up was 30 months.

Paper II is a retrospective single institutional study of patients treated between 1995 and 2012. Inclusion criteria were GTV volume of at least 70 cc (assuming a spherical tumor form, this volume corresponds to a diameter of about 5.1 cm), and curatively intended SBRT with a prescribed dose of at least 72 Gy BED ($\alpha/\beta = 10$Gy), corresponding to the fractionation of 8 Gy x 5. Patients without available radiation plans or clinical records were excluded. Finally, 164 patients with 175 tumors were included in the study. Median follow-up was 16.6 months. Median tumor volume was 173 cc, corresponding to a dimeter of a 6.4 cm spherical structure. 40 patients had a tumor within 1 cm from trachea or main bronchi. 48 tumors (29%) were of non-small cell lung cancer origin, while 32 (19%) and 29 (18%) were colorectal cancer (CRC) and renal cell cancer (RCC) respectively. The remaining cohort was of a mixed tumor origin.

Paper III is a prospective multi-center phase-2 non-randomized study (the HILUS study), conducted within nine centers in Sweden, Denmark and Norway between 2011 and 2016. Inclusion criteria was tumor location within 1 cm from any part of the distal 2 cm of trachea, main or lobar bronchi. The study treatment was a risk adapted SBRT protocol of 7Gyx8. Lesions larger than 5 cm were excluded. The cohort was divided into Group A, where tumors were located within 1 cm from trachea or main bronchi, while the Group B contained the rest of the tumors (i.e. more than 1 cm from main bronchi and trachea, but within 1 cm from lobar bronchi). 74 patients were included in the trial, whereof 65 were treated according to protocol

and included in the final analysis. 39 patients were in group A, while the remaining 26 patients were in group B.

Paper IV is an analysis of the merged cohort with 65 patients from the prospective study with addition of 167 retrospectively collected patients with tumors within 2 cm from the whole trachea, main or lobar bronchi and treated in the same way as in the prospective study but outside of it between 2010 and 2019. The patients came from five Scandinavian centers: Stockholm, Oslo, Gothenburg, Odense and Aarhus. The division between Group A and Group B was the same as in Study III, with the addition of Group C that included (1-2 cm from any part of the PBT) and group D (within 1 cm from proximal trachea only – tumors within 1 cm from the most distal 2 cm of the trachea belonged to group A)

Ethical permissions were granted by the ethical committee of Region Stockholm, by the diary numbers 2014/1581-31, 2021/2143-31/2, 2011/676-31/3 and 2015/1134-32 respectively.

3.2. Data retrieval

Clinical data on patient characteristics, diagnosis, clinical follow up, radiological reports and survival were obtained from the local medical records. For patients treated and radiologically followed in Stockholm, all images were reviewed in the local PACS system by the undersigned, evaluating local control and, when relevant, toxicity. In cases when direct image assessment was not possible, the assessment was made from radiological reports and decisions on multidisciplinary conferences, however some patients in Paper II were excluded from the local control analysis due to the lack of reliable data on radiological follow up. The dosimetry data was retrieved from the respective local radiation treatment planning software.

3.3. Risk organ delineation

In Paper I, III and IV, delineations of risk organs were performed. In Paper I, the risk organ was the brachial plexus ipsi-laterally to the treated tumor. As a part of preparation of the study design, a literature search was performed to find out if it is possible to perform a plexus brachialis delineation, to study the methodologies of the plexus delineation offered by other authors, as well as the existing criticism against these. Methodological studies of the anatomy of plexus brachialis on MRI and diagnostic contrast enhanced CT, were performed by the undersigned under the guidance of senior radiologists with the relevant competence. For the contouring, the existing RTOG-protocol for plexus brachialis was used, modified by the undersigned according to the needs of the current study.

To well visualize the anatomy of the cranial segments brachial plexus which runs along and between the muscles of the neck, an MRI is needed. However, in the context of SBRT of apically located lung tumors, the most important part of the brachial plexus is the caudal and lateral segments, which run on top of the lung, along the axillar and the brachial vessels, and are thus well defined on CT, framed by either contrast-bearing vessel structures, or subcutaneous fat (fig 17).

The delineation was performed on the dose plan CT images of 3 mm slice thickness, mostly without the contrast enhancement, which made the task clearly more difficult. However, the contrast enhanced thin slice diagnostic CT, or MRI, could be used in cases of anatomic uncertainties.

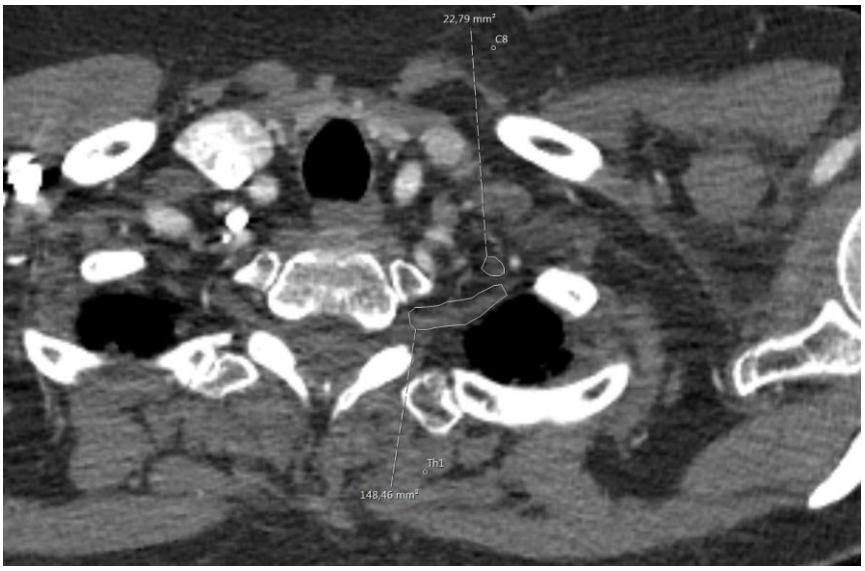

Fig 17. Th1-2 nerve root is one of the most important parts of the brachial plexus in the context of SBRT of apical lung tumors, here well visualized on diagnostic i.v. contrast enhanced CT, image slice thickness 0.6 mm

In Paper III and IV, the decision on separate delineation of each bronchial structure for further analysis was made by the multidisciplinary team in Stockholm, which was responsible for the planning and the conduction of the study. Subsequently, the lumen of the trachea, main bronchi, the intermediate bronchus, all lobar bronchi and lingula bronchus, were delineated separately. Two new structures were then created, one consisting of lumen of the trachea and the main bronchi, and one consisting of the lumen of the whole PBT. For each one of these two new structures addition margin of 2 mm was added, representing the contours of the bronchial wall. The latter four structures were then used for statistical analyses of correlation between dose-volume parameters and toxicity.

In paper III also esophagus, heart, aorta, pulmonary trunk as well as both pulmonary arteries, were delineated.

3.4. Dose characteristics

The standard SBRT fractionation in Stockholm, for tumors located far from organs at risk, is 15 Gy x 3, to 67% of the periphery of the PTV (see the introduction section for more details).

For fast growing tumors with $\alpha/\beta = 10$ Gy, this corresponds to BED to the whole tumor exceeding 100 Gy, calculated with to the Linear Quadratic (LQ) model. However, the fractionation may be adapted depending on proximity to sensitive organs; the current standard fractionation for large tumors or tumors in the proximity of moderately sensitive organs such as chest wall is 10 Gy x 5. The standard fractionation for radiation resistant tumors, such as CRC, is 17 Gy x 3. In Paper I, the median dose per fraction was 15 Gy and the median number of fractions was 3. In Paper II, a very wide range of fractionation regimes were used, which reflects the difficulty of treating tumors of that size, with the median fractional dose of 10 Gy and the median number of fractions of 4. In Paper III and IV, all patients received the same fractionation of 7 Gy x 8, corresponding to a BED of 95.2 Gy.

Paper I, III and IV presents detailed data to the organs at risk. All BED and EQD2 to the risk organs were recalculated with assumed normal tissue α/β value of 3 Gy. In Paper I, the maximal punctual dose to the risk organ, as well as the lowest dose lever to the "hottest" 0.1 cc, 1 cc and 3 cc of the structure, are used in the statistical calculations of the relationship between dose and toxicity. In paper III and IV, maximal punctual dose as well as minimal doses to the "hottest" 0.01 cc, 0.2 cc, 0.5 cc and 1 cc in the bronchial structures were used. Additionally, for paper I Single Fraction Equivalent Dose (SFED) is calculated using the Universal Survival Curve model (USC).

In Paper II, minimal, mean and maximal BED to the GTV were used for statistical analyzes as potential predictive markers for local recurrence. All BED were recalculated with the assumed tumor α/β value of 10 Gy.

In all papers, the Linear-Quadratic model (LQ) is used to calculate the biologically effective dose (BED) and EQD2. When BED is presented for $\alpha/\beta = 10$ Gy, it usually refers to fast growing tumors, such as NSCLC. When BED or EQD2 is presented for an $\alpha/\beta = 3$ Gy, it usually refers to the risk organs.

3.5. Toxicity

In Paper I, II, III and IV, all adverse events are graded according to the CTCAE 4.0 or 5.0. In case of radiation induced brachial plexopathy (RIBP), which was the scope of Paper I, there exists no grade 4 or grade 5 adverse event in CTCAE 4.0 (i.e. no symptoms that are potentially life threatening or fatal). It may be questioned, to what extent retrospective collection of grade 2-3 symptoms is reliable. However, in case of RIBP, even mild symptoms have a major effect on the patient's life and are thus usually documented in the medical records. In Paper II, having the retrospective design of the study in mind, only grade 3 or higher side effects are collected. In Paper III all adverse events (grade 1-5) are collected prospectively and reported. In study IV, all patients were treated at large centers, however several patients were followed by local hospitals, leading to heterogeneity of documentation of mild adverse events. Even though toxicity for of all grades (1-5) is collected and presented in the paper, the focus is mainly on grade 5 toxicity in general, and on grade 5 lung hemorrhages specifically.

Grade 5 adverse events are defined as events that probably or certainly could be linked to SBRT. In all papers, all uncertain cases of grade 5 events were discussed multidisciplinary.

3.6. Statistical analyses

In Paper I, NTCP-modelling was performed for the outcome ≥grade 2 RIBP. The dose-volume parameters used were converted both to BED and SFED (i.e. using both the LQ-model and the USC-model). As a measure of model performance, AUC were calculated.

In Paper II, the chi-square or Fischer's exact test were used for variables in contingency tables. Locon control rates were estimated by Kaplan-Meier method. Time-dependent variables were evaluated by Cox regression analyses.

In Paper III, for variables in contingency tables the chi-square or Fischer's exact test were used. KM-method was used to estimate OS. Logistic regression was performed for calculating used for modulation of risk of grade 5 bronchial bleeding vs bronchial dose.

In Paper IV, predicting factors for grade 5 toxicity and bleeding were analyzed with Univariate Cox Regression models. OS was estimated by the KM-method. The cumulative hazard for grade 5 toxicity and grade 5 bleeding was estimated using Aalen-Johansen estimates, and Cox regression was used to estimate the hazard ratio.

1. Results and discussion

1.1. Radiation-induced brachial plexus toxicity after SBRT of apically located lung lesions (Paper I)

In this cohort 52 tumors with 56 treated tumors and 55 brachial plexuses at risk were analyzed. Seven of the patients developed radiation induced brachial plexopathy (RIBP), of which four patients up to grade three, and the remaining patients grade two. Six patients had RIBP in the form of pain, while three had motor- or/and neurological symptom. Two patients had both pain and neurological symptoms. The first signs of symptom appeared at median time of 8.7 months after SBRT. One additional patients developed symptoms from brachial plexus following a massive local tumor recurrence, with overgrowth over the plexus, which was judged not to be related to the radiotherapy. Median follow-up and median survival were 30 months. The prescription doses for the seven patients that developed RIBP were 96-113 Gy BED (α/β=10 Gy), where 100 Gy is the commonly accepted ablative dose for most cancers, prescribed to the periphery of the PTV. None of the patients with RIBP experienced local recurrence. Six of seven patients with RIPB have received a dose of > 130 Gy (α/β=3 Gy). None of the patients with RIBP had diabetes or received neurotoxic chemotherapy, which potentially could explain the symptoms. On the average, the patents with RIBP had shorter distance to plexus (4 mm vs 24 mm).

The NTCP-modelling showed good fit both for BED and for SFED, where maximum punctual doses has shown the best correlation between development of RIBP and radiation dose, however not reaching the statistical significance ($p > 0.05$). No difference was seen between the LQ-model and the Universal Survival Curve (USC) model, why all the results are presented according to the LQ model (i.e. with BED). For the maximum punctual dose of 130 Gy (α/β = 3 Gy), the NTCP-model predicted a complication probability of <10%. Hence, for a 3-fractions treatment, the true tolerable maximal punctual physical dose in probably >26Gy, and we suggest the dose of ≤30 Gy as a reasonable constraint for dose planning.

Interestingly, 10 of the patients in the cohort with a median follow-up at 19 months, receiving a maximum punctual dose to the brachial plexus > 130 Gy BED ($\alpha/\beta = 3$ Gy), did not develop RIBP. This may be explained by several factors including individual radiosensitivity, underreporting of the symptoms, short follow-up time and uncertainty in the delineation. The brachial plexus is a thin structure that runs along several longitudinal structures of varying attenuation, making its visualization sensitive to slice thickness, contrast phase and artefacts. Although the study only applies to the inferior-lateral aspects of the plexus that are relatively well visible on the CT, and despite that diagnostic CT with thin sliced and i.v. contrast, or MRI, was available to use for anatomic comparisons, the small margins in both SBRT and brachial plexus anatomy is still problematic in this context, where it cannot be ruled out that mistakes in contouring could affect the study outcome. Furthermore, although apical parts of the lungs have limited motions during the breathing cycle, small changes in position that are hard to correct for, cannot be completely ruled out. Hence, we propose that a planning organ at risk volume (PRV) in the form of a 2-mm margin around the plexus, may be used with a planning dose constraint of 170 Gy.

Other important limitations to this study is the small size of the cohort and the retrospective character of the study, which may have led to that some cases of RIBP had not been detected.

1.2. Extending hypofractionated stereotactic body radiotherapy to tumours larger than 70cc – effects and side effects (Paper II)

In total, 164 patients with 175 tumors were included in the study. Median follow-up and overall survival was 16.6 months. Evaluable for local control were 165 tumors in 154 patients. 40 tumors, in 38 patients, were located near the PBT. The median GTV volume was 137 cc. The median prescribed BED (α/β=10 Gy) was 80 Gy.

Minimal, mean and maximum doses to GTV were all statistically significant for local control in univariate analyses, but in multivariate analyses only the minimal dose remained a statistically significant dose-volume parameter. Also, tumor histology was significant for

local control in both uni- and multivariate analyzes, with the best local control for renal cell cancer (RCC) and worst for colorectal cancer (CRC). No other parameters, including the GTV volume or tumor location, were statistically significant for local control. Two years' local control for RCC and CRC was 94% and 18% respectively. Two years' local control for NSCLC was 48%, which is substantially lower than for peripherally located small NSCLC, where local control in most studies varies between 90-98%. Likewise, local control in our cohort was lower compared to other studies on SBRT of NSCLC > 5 cm (128-131), which can be partly explained by larger tumors masses in our cohort compared to the referred series, and partly by the fact that many tumors in our cohort received a prescribed BED (α/β=10 Gy) of substantially lower than 100 Gy.

There were ten cases of possible or certain grade 5 toxicity, whereof 4 cases of lethal hemoptysis, 4 cases of radiation pneumonitis, one gastro-intestinal bleeding and one duodenal perforation. Among 8 cases of lung related toxicity, seven patients had tumors with a central thoracic location, while one patient had a peripheral lung tumor. All patients with lethal hemoptysis had centrally located thoracic tumors. In both cases of gastro-intestinal grade 5 toxicity, the tumors were in the liver. No statistical analyzes were performed regarding grade 5 toxicities due to low number of cases, however the clear majority of cases occurred in the cohort with centrally located thoracic tumors.

For tumors of large size but far from risk organs, where sufficient radiation dose is possible to deliver to the whole tumor volume, SBRT may be a valuable treatment option. Our study has confirmed colorectal cancer to be a more radiation resistant histology compared to NSCLC. For large CRC, other treatment modalities than SBRT should be preferred.

The limitations of this study were its retrospective nature, the heterogeneity of the cohort regarding tumor histology, treatment dose, tumor location and the treatment technique, as well as limited follow-up. However, several of the study's weaknesses are also its strengths. The presence of several comparably large cohorts of major tumor histologies, a high rate of local recurrence and wide spectrum of prescribed radiation dose, makes it easier to statistically analyze dependence between dose, histology and tumor control.

1.3. The HILUS-trial – a prospective Nordic multi-center phase II study of ultra-central lung tumors treated with stereotactic body radiotherapy (Paper III)

Out of 74 patients included, 65 patients (68 tumors) were treated according to the protocol. 24 patients had tumors located 5 mm or less from the main bronchus, 15 patients – 6-10 mm from main bronchus and finally 26 patients – tumors more than 10 mm from main bronchus. The local control at 3 years was 83%.

Ten patients experienced possible grade 5 events, including eight cases of lethal hemoptysis, one case of radiation pneumonitis and one case of trachea-esophageal fistula. No patient with grade 5 bleeding had any radiological signs of local recurrence.

Univariate analyses showed that distance between tumor and main bronchus is correlated to grade 5 adverse event ($p<0.05$). One patient of 26 (4%) in the group B, and seven patients of 39 (18%) in group A, died of hemoptysis. Dose to the structure consisting of the lumen of the trachea and the main bronchi, was the best predictor for grade 5 lung hemorrhage. Based on dose-volume modulations, it has been hypothesized that group B patients can be treated safely given that the maximum point dose (Dmax) to trachea and main bronchi does not exceed 70-80 Gy EQD2. Due to the small sample size, no definitive conclusions of the radiosensitivity of the central bronchi could be drawn.

1.4. HILUS III: A pooled analysis of risk factors for toxicity of SBRT of centrally and ultra-centrally located lung tumors (Paper IV)

The merged cohort consisted of 232 patients, whereof 108 patients in group A, 84 patients in group B, 35 patients in group C and five patients in group D. The median shortest distance to any part of the PBT was 2 mm, and the median shortest distance to a main bronchus was 12 mm. Nineteen patients had a tumor compression of any part of trachea, main or lobar bronchi.

Grade 5 toxicity was recorded in 30 patients, whereof one patient in group A had both a grade 5 lung hemorrhage and a possible grade 5 lung infection. 20 patients with grade 5 toxicity were in group A, eight were in group B and two patients in group C. There were totally 21 grade 5 hemorrhages, whereof 15 in group A and 6 in group B. Both possible grade 5 events in group C (COPD exacerbation and cardiac failure) are unspecific in the context of the SBRT, and dubiously represent dose-related bronchial toxicity.

Distance to main and lobar bronchi, as well as several dose-volume parameters to main bronchi fell out significant for both grade 5 toxicity in general, and grade 5 lung hemorrhage specifically in univariate analyses. Also, bronchial compression of any part of the trachea, main or lobar bronchi showed clear statistical significance for grade 5 toxicity and grade 5 bleeding.

Interestingly, six of eight grade 5 events in the group B were within 1 cm from the intermediate bronchus. Also, five patients with a grade 5 bleeding or infection had a near-to-maximum dose (D0.001cc) to a trachea or main bronchus of less than 60Gy EQD2, which is clearly below the high-risk threshold of 70-80 Gy EQD2 stated in the hypothesis from the prospective HILUS study. On the other hand, all these five patients had a near-to-maximum dose to the intermediate bronchus of >92 Gy.

During the design of the study, the intermediate bronchus was classified as a lobar bronchus though its size significantly exceeds the size of other lobar bronchi. Our data suggest that the radiation sensitivity of the intermediate bronchus may be closer to the radiation sensitivity of the main bronchi than the rest of the lobar bronchi. Detailed dose-volume modulation of the individual radiation sensitivity of each part of the bronchial tree is warranted to determine the exact dose constraints for each bronchus, to avoid grade 5 toxic events.

Three years' local control and overall survival were 82% and 39% respectively, which is in line with what is expected for this fragile patient cohort, also given that the treatment fractionation resulted in a BED slightly below 100 Gy. There was no difference between local control and survival between the study groups.

2. Conclusions

In *Paper I*, dose-volume parameters and toxicity related to brachial plexus, and based on our results, propose that maximum dose to the plexus should be kept below 30Gy (maximum punctual risk organ BED = 130Gy).

In *Paper II*, we study factors that affect local control of very large tumors treated with SBRT, where we find minimal radiation dose and histology to be the two most important factors. For carefully chosen patients with very large tumors, SBRT represents a valuable treatment option. Also, we confirm that tumor location close to central bronchial structures, is strongly predictive for lethal adverse events.

In *Paper III*, we report on a prospective multicenter trial on SBRT of centrally located tumors. Distance to main bronchi as well as dose to lumen of trachea/main bronchi is predictive factor for lethal adverse events. The study results give rise to the hypothesis that tumors with a distance to trachea or main bronchus of larger than 1 cm, may be treated without excessive risk of grade 5 event given that the maximum point dose to trachea and main bronchi does not exceed 70-80 Gy EQD2.

In *Paper IV*, we report data from a broaden statistical base, that partly contradict and correct the above-stated hypothesis. Several patients with targets >1 cm from trachea and main bronchi, and with maximum doses to these structures <70-80 Gy EQD2, have experienced grade 5 adverse events. However, the hypothesis can still hold if the concept of high-risk bronchial tree is extended to include the intermediate bronchus. Dose-volume modulations of individual parts of the PBT are warranted. SBRT of tumors that compress any part of the PBT should be avoided.

3. Future Perspectives

Long-term development of individualized SBRT is strongly dependent on large-scale multi-center studies, where means of dose prescriptions and reporting (to both target and risk organs) must be harmonized between different centers. This applies to both target and risk organs, where a uniform system for delineation is needed for risk organs, as well as individual parts of the risk organs. Further, a robust uniform system for controlling the delivered dose (i.e. that the delivered dose corresponds to the prescribed dose, and if not – to what extent?) is urgently needed.

The radiological follow-up regarding chronic inflammation, weakening of the bronchial walls, local vascular proliferation and growth of small arteries into the sight of the damaged tissues, could potentially be improved if these processes could be better visualized, which may be possible with increased use of photon-counting CT technique (132).

Radiation sensitivity of individual tumors – and tumor sub-volumes – needs to be further studied. Despite the recent years' improvements in imaging, patient fixation and dose delivery techniques, the local control after SBRT in most series is still below 100%. Causes of the local recurrences need to be better understood; radiation resistant tumors or tumor areas need to be managed with an increased radiation dose or otherwise, while the more radiation-sensitive tumors may offer a room for maneuver in compromising the target coverage for saving proximal risk organs. Large-scale studies of biological properties that can mediate radiation resistance (such as hypoxia) should be initiated.

The potential systemic immunological effect of SBRT need to be better exploited, not least in combination with systemic treatments such as immunotherapy. Immunological mechanisms of radiotherapy need to be better understood, and immunological biomarkers to be developed, including using serial PET/CT and tumor biopsies.

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References

1. Blomgren H, Lax I, Naslund I, Svanstrom R. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol. 1995;34(6):861-70.
2. Lax I, Blomgren H, Naslund I, Svanstrom R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. Acta Oncol. 1994;33(6):677-83.
3. Loganadane G, Martinetti F, Mercier O, Krhili S, Riet FG, Mbagui R, et al. Stereotactic ablative radiotherapy for early stage non-small cell lung cancer: A critical literature review of predictive factors of relapse. Cancer Treat Rev. 2016;50:240-6.
4. Baumann P, Nyman J, Lax I, Friesland S, Hoyer M, Rehn Ericsson S, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. Acta Oncol. 2006;45(7):787-95.
5. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol. 2009;27(20):3290-6.
6. Qiao X, Tullgren O, Lax I, Sirzen F, Lewensohn R. The role of radiotherapy in treatment of stage I non-small cell lung cancer. Lung Cancer. 2003;41(1):1-11.
7. Bradley J. A review of radiation dose escalation trials for non-small cell lung cancer within the Radiation Therapy Oncology Group. Semin Oncol. 2005;32(2 Suppl 3):S111-3.
8. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys. 2011;81(5):1352-8.
9. Kavanagh BD, Schefter TE, Cardenes HR, Stieber VW, Raben D, Timmerman RD, et al. Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. Acta Oncol. 2006;45(7):848-55.
10. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol. 2007;2(7 Suppl 3):S94-100.
11. Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys. 2009;75(3):677-82.
12. Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys. 2005;63(5):1427-31.
13. Nyman J, Hallqvist A, Lund JA, Brustugun OT, Bergman B, Bergstrom P, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiother Oncol. 2016;121(1):1-8.
14. Narita A, Takeda A, Eriguchi T, Saigusa Y, Sanuki N, Tsurugai Y, et al. Stereotactic body radiotherapy for primary non-small cell lung cancer patients with clinical T3-4N0M0 (UICC 8th edition): outcomes and patterns of failure. J Radiat Res. 2019;60(5):639-49.
15. Duijm M, Tekatli H, Oomen-de Hoop E, Verbakel W, Schillemans W, Slotman BJ, et al. Esophagus toxicity after stereotactic and hypofractionated radiotherapy for central lung tumors: Normal tissue complication probability modeling. Radiother Oncol. 2018;127(2):233-8.
16. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol. 2006;24(30):4833-9.
17. Zhao L, Zhou S, Balter P, Shen C, Gomez DR, Welsh JD, et al. Planning Target Volume D95 and Mean Dose Should Be Considered for Optimal Local Control for Stereotactic Ablative Radiation Therapy. Int J Radiat Oncol Biol Phys. 2016;95(4):1226-35.

18. Moreno AC, Fellman B, Hobbs BP, Liao Z, Gomez DR, Chen A, et al. Biologically Effective Dose in Stereotactic Body Radiotherapy and Survival for Patients with Early-Stage Non-Small Cell Lung Cancer. J Thorac Oncol. 2019.
19. Videtic GM, Hu C, Singh AK, Chang JY, Parker W, Olivier KR, et al. A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer: NRG Oncology RTOG 0915 (NCCTG N0927). Int J Radiat Oncol Biol Phys. 2015;93(4):757-64.
20. Kestin L, Grills I, Guckenberger M, Belderbos J, Hope AJ, Werner-Wasik M, et al. Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. Radiother Oncol. 2014;110(3):499-504.
21. Videtic GMM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol. 2017;7(5):295-301.
22. Tandberg DJ, Tong BC, Ackerson BG, Kelsey CR. Surgery versus stereotactic body radiation therapy for stage I non-small cell lung cancer: A comprehensive review. Cancer. 2018;124(4):667-78.
23. Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, et al. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys. 2015;93(5):989-96.
24. Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16(6):630-7.
25. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8-10.
26. Palma DA, Salama JK, Lo SS, Senan S, Treasure T, Govindan R, et al. The oligometastatic state - separating truth from wishful thinking. Nat Rev Clin Oncol. 2014;11(9):549-57.
27. Gomez DR, Blumenschein GR, Jr., Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016;17(12):1672-82.
28. Lo SS, Teh BS, Mayr NA, Olencki TE, Wang JZ, Grecula JC, et al. Stereotactic body radiation therapy for oligometastases. Discov Med. 2010;10(52):247-54.
29. Gomez DR, Tang C, Zhang J, Blumenschein GR, Jr., Hernandez M, Lee JJ, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol. 2019;37(18):1558-65.
30. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. J Clin Oncol. 2020;38(25):2830-8.
31. Li Y, Dykstra M, Best TD, Pursley J, Chopra N, Keane FK, et al. Differential inflammatory response dynamics in normal lung following stereotactic body radiation therapy with protons versus photons. Radiother Oncol. 2019;136:169-75.
32. Dahele M, Palma D, Lagerwaard F, Slotman B, Senan S. Radiological changes after stereotactic radiotherapy for stage I lung cancer. J Thorac Oncol. 2011;6(7):1221-8.
33. Febbo JA, Gaddikeri RS, Shah PN. Stereotactic Body Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer: A Primer for Radiologists. Radiographics. 2018;38(5):1312-36.
34. Zhang X, Liu H, Balter P, Allen PK, Komaki R, Pan T, et al. Positron emission tomography for assessing local failure after stereotactic body radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2012;83(5):1558-65.
35. Schwartz LH, Litiere S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer. 2016;62:132-7.

36. Vernuccio F, Godfrey D, Meyer M, Williamson HV, Salama JK, Niedzwiecki D, et al. Local Tumor Control and Patient Outcome Using Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: iRECIST as a Potential Substitute for Traditional Criteria. AJR Am J Roentgenol. 2019;213(6):1232-9.
37. Mattonen SA, Ward AD, Palma DA. Pulmonary imaging after stereotactic radiotherapy-does RECIST still apply? Br J Radiol. 2016;89(1065):20160113.
38. Tetreau R, Llacer C, Riou O, Deshayes E. Evaluation of response after SBRT for liver tumors. Rep Pract Oncol Radiother. 2017;22(2):170-5.
39. Thompson M, Rosenzweig KE. The evolving toxicity profile of SBRT for lung cancer. Transl Lung Cancer Res. 2019;8(1):48-57.
40. De Rose F, Franceschini D, Reggiori G, Stravato A, Navarria P, Ascolese AM, et al. Organs at risk in lung SBRT. Phys Med. 2017;44:131-8.
41. De La Pinta Alonso C. Radiation-induced liver disease in the era of SBRT: a review. Expert Rev Gastroenterol Hepatol. 2020;14(12):1195-201.
42. Brunner TB, Nestle U, Grosu AL, Partridge M. SBRT in pancreatic cancer: what is the therapeutic window? Radiother Oncol. 2015;114(1):109-16.
43. Baumann BC, Wei J, Plastaras JP, Lukens JN, Damjanov N, Hoteit M, et al. Stereotactic Body Radiation Therapy (SBRT) for Hepatocellular Carcinoma: High Rates of Local Control With Low Toxicity. Am J Clin Oncol. 2018;41(11):1118-24.
44. Arnett ALH, Mou B, Owen D, Park SS, Nelson K, Hallemeier CL, et al. Long-term Clinical Outcomes and Safety Profile of SBRT for Centrally Located NSCLC. Adv Radiat Oncol. 2019;4(2):422-8.
45. Roesch J, Panje C, Sterzing F, Mantel F, Nestle U, Andratschke N, et al. SBRT for centrally localized NSCLC - What is too central? Radiat Oncol. 2016;11(1):157.
46. Giuliani M, Mathew AS, Bahig H, Bratman SV, Filion E, Glick D, et al. SUNSET: Stereotactic Radiation for Ultracentral Non-Small-Cell Lung Cancer-A Safety and Efficacy Trial. Clin Lung Cancer. 2018;19(4):e529-e32.
47. Wu AJ, Williams E, Modh A, Foster A, Yorke E, Rimner A, et al. Dosimetric predictors of esophageal toxicity after stereotactic body radiotherapy for central lung tumors. Radiother Oncol. 2014;112(2):267-71.
48. Singh R, Ansinelli H, Sharma D, Jenkins J, Davis J, Sharma S, et al. Stereotactic body radiation therapy (SBRT) for metastatic renal cell carcinoma: A multi-institutional experience. J Radiosurg SBRT. 2020;7(1):29-37.
49. Stephans KL, Djemil T, Tendulkar RD, Robinson CG, Reddy CA, Videtic GM. Prediction of chest wall toxicity from lung stereotactic body radiotherapy (SBRT). Int J Radiat Oncol Biol Phys. 2012;82(2):974-80.
50. Sandler KA, Veruttipong D, Agopian VG, Finn RS, Hong JC, Kaldas FM, et al. Stereotactic body radiotherapy (SBRT) for locally advanced extrahepatic and intrahepatic cholangiocarcinoma. Adv Radiat Oncol. 2016;1(4):237-43.
51. Reshko LB, Richardson MK, Spencer K, Kersh CR. Stereotactic Body Radiation Therapy (SBRT) in Pelvic Lymph Node Oligometastases. Cancer Invest. 2020;38(10):599-607.
52. Lindberg K, Onjukka E. Medical consequences of radiation exposure of the bronchi-what can we learn from high-dose precision radiation therapy? J Radiol Prot. 2021;41(4).
53. Tekatli H, Senan S, Dahele M, Slotman BJ, Verbakel WF. Stereotactic ablative radiotherapy (SABR) for central lung tumors: Plan quality and long-term clinical outcomes. Radiother Oncol. 2015;117(1):64-70.
54. Senthi S, Haasbeek CJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol. 2013;106(3):276-82.
55. Rim CH, Kim Y, Kim CY, Yoon WS, Yang DS. Is stereotactic body radiotherapy for ultra-central lung tumor a feasible option? A systemic review and meta-analysis. Int J Radiat Biol. 2019;95(3):329-37.

56. Chen H, Laba JM, Zayed S, Boldt RG, Palma DA, Louie AV. Safety and Effectiveness of Stereotactic Ablative Radiotherapy for Ultra-Central Lung Lesions: A Systematic Review. J Thorac Oncol. 2019;14(8):1332-42.
57. Tekatli H, Haasbeek N, Dahele M, De Haan P, Verbakel W, Bongers E, et al. Outcomes of Hypofractionated High-Dose Radiotherapy in Poor-Risk Patients with "Ultracentral" Non-Small Cell Lung Cancer. J Thorac Oncol. 2016;11(7):1081-9.
58. Haseltine JM, Rimner A, Gelblum DY, Modh A, Rosenzweig KE, Jackson A, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. Pract Radiat Oncol. 2016;6(2):e27-33.
59. Horne ZD, Richman AH, Dohopolski MJ, Clump DA, Burton SA, Heron DE. Stereotactic body radiation therapy for isolated hilar and mediastinal non-small cell lung cancers. Lung Cancer. 2018;115:1-4.
60. Yang D, Cui J, Zhao J, You J, Yu R, Yu H, et al. Stereotactic ablative radiotherapy of 60 Gy in eight fractions is safe for ultracentral non-small cell lung cancer. Thorac Cancer. 2020;11(3):754-61.
61. Lenglet A, Campeau MP, Mathieu D, Bahig H, Lambert L, Vu T, et al. Risk-adapted stereotactic ablative radiotherapy for central and ultra-central lung tumours. Radiother Oncol. 2019;134:178-84.
62. Chang JH, Poon I, Erler D, Zhang L, Cheung P. The safety and effectiveness of stereotactic body radiotherapy for central versus ultracentral lung tumors. Radiother Oncol. 2018;129(2):277-83.
63. Raman S, Yau V, Pineda S, Le LW, Lau A, Bezjak A, et al. Ultracentral Tumors Treated With Stereotactic Body Radiotherapy: Single-Institution Experience. Clin Lung Cancer. 2018;19(5):e803-e10.
64. Lischalk JW, Malik RM, Collins SP, Collins BT, Matus IA, Anderson ED. Stereotactic body radiotherapy (SBRT) for high-risk central pulmonary metastases. Radiat Oncol. 2016;11:28.
65. Zhao Y, Khawandanh E, Thomas S, Zhang S, Dunne EM, Liu M, et al. Outcomes of stereotactic body radiotherapy 60 Gy in 8 fractions when prioritizing organs at risk for central and ultracentral lung tumors. Radiat Oncol. 2020;15(1):61.
66. Karlsson K, Nyman J, Baumann P, Wersall P, Drugge N, Gagliardi G, et al. Retrospective cohort study of bronchial doses and radiation-induced atelectasis after stereotactic body radiation therapy of lung tumors located close to the bronchial tree. Int J Radiat Oncol Biol Phys. 2013;87(3):590-5.
67. Tekatli H, Duijm M, Oomen-de Hoop E, Verbakel W, Schillemans W, Slotman BJ, et al. Normal Tissue Complication Probability Modeling of Pulmonary Toxicity After Stereotactic and Hypofractionated Radiation Therapy for Central Lung Tumors. Int J Radiat Oncol Biol Phys. 2018;100(3):738-47.
68. Chaudhuri AA, Tang C, Binkley MS, Jin M, Wynne JF, von Eyben R, et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. Lung Cancer. 2015;89(1):50-6.
69. Song SY, Choi W, Shin SS, Lee SW, Ahn SD, Kim JH, et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. Lung Cancer. 2009;66(1):89-93.
70. Unger K, Ju A, Oermann E, Suy S, Yu X, Vahdat S, et al. CyberKnife for hilar lung tumors: report of clinical response and toxicity. J Hematol Oncol. 2010;3:39.
71. Lindberg K, Grozman V, Karlsson K, Lindberg S, Lax I, Wersall P, et al. The HILUS-trial - a prospective Nordic multi-center phase II study of ultra-central lung tumors treated with stereotactic body radiotherapy. J Thorac Oncol. 2021.
72. Amador C, Weber C, Varacallo M. Anatomy, Thorax, Bronchial. StatPearls. Treasure Island (FL)2022.
73. Ball M, Hossain M, Padalia D. Anatomy, Airway. StatPearls. Treasure Island (FL)2022.

74. Armstrong WB, Netterville JL. Anatomy of the larynx, trachea, and bronchi. Otolaryngol Clin North Am. 1995;28(4):685-99.
75. Mehran RJ. Fundamental and Practical Aspects of Airway Anatomy: From Glottis to Segmental Bronchus. Thorac Surg Clin. 2018;28(2):117-25.
76. Minnich DJ, Mathisen DJ. Anatomy of the trachea, carina, and bronchi. Thorac Surg Clin. 2007;17(4):571-85.
77. Petagna L, Antonelli A, Ganini C, Bellato V, Campanelli M, Divizia A, et al. Pathophysiology of Crohn's disease inflammation and recurrence. Biol Direct. 2020;15(1):23.
78. Saers SJ, Scheltinga MR. Primary aortoenteric fistula. Br J Surg. 2005;92(2):143-52.
79. Yamashita H, Takahashi W, Haga A, Nakagawa K. Radiation pneumonitis after stereotactic radiation therapy for lung cancer. World J Radiol. 2014;6(9):708-15.
80. Liu Y, Wang W, Shiue K, Yao H, Cerra-Franco A, Shapiro RH, et al. Risk factors for symptomatic radiation pneumonitis after stereotactic body radiation therapy (SBRT) in patients with non-small cell lung cancer. Radiother Oncol. 2020;156:231-8.
81. Hanania AN, Mainwaring W, Ghebre YT, Hanania NA, Ludwig M. Radiation-Induced Lung Injury: Assessment and Management. Chest. 2019;156(1):150-62.
82. Stam B, Peulen H, Guckenberger M, Mantel F, Hope A, Werner-Wasik M, et al. Dose to heart substructures is associated with non-cancer death after SBRT in stage I-II NSCLC patients. Radiother Oncol. 2017;123(3):370-5.
83. Piroth MD, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, et al. Heart toxicity from breast cancer radiotherapy : Current findings, assessment, and prevention. Strahlenther Onkol. 2019;195(1):1-12.
84. Wang K, Eblan MJ, Deal AM, Lipner M, Zagar TM, Wang Y, et al. Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. J Clin Oncol. 2017;35(13):1387-94.
85. Ferrante MA. Brachial plexopathies: classification, causes, and consequences. Muscle Nerve. 2004;30(5):547-68.
86. Forquer JA, Fakiris AJ, Timmerman RD, Lo SS, Perkins SM, McGarry RC, et al. Brachial plexopathy from stereotactic body radiotherapy in early-stage NSCLC: dose-limiting toxicity in apical tumor sites. Radiother Oncol. 2009;93(3):408-13.
87. Amini A, Yang J, Williamson R, McBurney ML, Erasmus J, Jr., Allen PK, et al. Dose constraints to prevent radiation-induced brachial plexopathy in patients treated for lung cancer. Int J Radiat Oncol Biol Phys. 2012;82(3):e391-8.
88. Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, et al. Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma. J Clin Oncol. 2016;34(5):452-9.
89. Steel GG, McMillan TJ, Peacock JH. The 5Rs of radiobiology. Int J Radiat Biol. 1989;56(6):1045-8.
90. Trott KR. Experimental results and clinical implications of the four R's in fractionated radiotherapy. Radiat Environ Biophys. 1982;20(3):159-70.
91. Gray LH, Conger AD, Ebert M, Hornsey S, Scott OC. The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Br J Radiol. 1953;26(312):638-48.
92. Brown JM, Wilson WR. Exploiting tumour hypoxia in cancer treatment. Nat Rev Cancer. 2004;4(6):437-47.
93. Rodriguez-Barbeito P, Diaz-Botana P, Gago-Arias A, Feijoo M, Neira S, Guiu-Souto J, et al. A Model of Indirect Cell Death Caused by Tumor Vascular Damage after High-Dose Radiotherapy. Cancer Res. 2019;79(23):6044-53.
94. Song CW, Kim MS, Cho LC, Dusenbery K, Sperduto PW. Radiobiological basis of SBRT and SRS. Int J Clin Oncol. 2014;19(4):570-8.

95. Song CW, Lee YJ, Griffin RJ, Park I, Koonce NA, Hui S, et al. Indirect Tumor Cell Death After High-Dose Hypofractionated Irradiation: Implications for Stereotactic Body Radiation Therapy and Stereotactic Radiation Surgery. Int J Radiat Oncol Biol Phys. 2015;93(1):166-72.
96. Park HJ, Griffin RJ, Hui S, Levitt SH, Song CW. Radiation-induced vascular damage in tumors: implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). Radiat Res. 2012;177(3):311-27.
97. Song CW, Glatstein E, Marks LB, Emami B, Grimm J, Sperduto PW, et al. Biological Principles of Stereotactic Body Radiation Therapy (SBRT) and Stereotactic Radiation Surgery (SRS): Indirect Cell Death. Int J Radiat Oncol Biol Phys. 2019.
98. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Oncol Biol Phys. 2014;88(2):254-62.
99. Sperduto PW, Song CW, Kirkpatrick JP, Glatstein E. A hypothesis: indirect cell death in the radiosurgery era. Int J Radiat Oncol Biol Phys. 2015;91(1):11-3.
100. Garelli E, Rittmeyer A, Putora PM, Glatzer M, Dressel R, Andreas S. Abscopal effect in lung cancer: three case reports and a concise review. Immunotherapy. 2019;11(17):1445-61.
101. Theelen W, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts J, et al. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019.
102. Ashrafizadeh M, Farhood B, Eleojo Musa A, Taeb S, Rezaeyan A, Najafi M. Abscopal effect in radioimmunotherapy. Int Immunopharmacol. 2020;85:106663.
103. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Brief report: Three-year overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC - Update from PACIFIC. J Thorac Oncol. 2019.
104. Bentzen SM, Thames HD. Tumor volume and local control probability: clinical data and radiobiological interpretations. Int J Radiat Oncol Biol Phys. 1996;36(1):247-51.
105. Bral S, Gevaert T, Linthout N, Versmessen H, Collen C, Engels B, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a Phase II trial. Int J Radiat Oncol Biol Phys. 2011;80(5):1343-9.
106. McGarry RC, Papiez L, Williams M, Whitford T, Timmerman RD. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. Int J Radiat Oncol Biol Phys. 2005;63(4):1010-5.
107. Allibhai Z, Taremi M, Bezjak A, Brade A, Hope AJ, Sun A, et al. The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2013;87(5):1064-70.
108. Davis JN, Medbery C, 3rd, Sharma S, Perry D, Pablo J, D'Ambrosio DJ, et al. Stereotactic body radiotherapy for early-stage non-small cell lung cancer: clinical outcomes from a National Patient Registry. J Radiat Oncol. 2015;4(1):55-63.
109. Kohutek ZA, Wu AJ, Zhang Z, Foster A, Din SU, Yorke ED, et al. FDG-PET maximum standardized uptake value is prognostic for recurrence and survival after stereotactic body radiotherapy for non-small cell lung cancer. Lung Cancer. 2015;89(2):115-20.
110. Hobbs CJ, Ko SJ, Paryani NN, Accurso JM, Olivier KR, Garces YI, et al. Stereotactic Body Radiotherapy for Medically Inoperable Stage I-II Non-Small Cell Lung Cancer: The Mayo Clinic Experience. Mayo Clin Proc Innov Qual Outcomes. 2018;2(1):40-8.
111. Lovinfosse P, Janvary ZL, Coucke P, Jodogne S, Bernard C, Hatt M, et al. FDG PET/CT texture analysis for predicting the outcome of lung cancer treated by stereotactic body radiation therapy. Eur J Nucl Med Mol Imaging. 2016;43(8):1453-60.
112. Takeda A, Kunieda E, Ohashi T, Aoki Y, Koike N, Takeda T. Stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer and other primary cancers in comparison with primary lung cancer. Radiother Oncol. 2011;101(2):255-9.

113. Joo JH, Park JH, Kim JC, Yu CS, Lim SB, Park IJ, et al. Local Control Outcomes Using Stereotactic Body Radiation Therapy for Liver Metastases From Colorectal Cancer. Int J Radiat Oncol Biol Phys. 2017;99(4):876-83.
114. Jingu K, Matsushita H, Yamamoto T, Umezawa R, Ishikawa Y, Takahashi N, et al. Stereotactic Radiotherapy for Pulmonary Oligometastases From Colorectal Cancer: A Systematic Review and Meta-Analysis. Technol Cancer Res Treat. 2018;17:1533033818794936.
115. Scorsetti M, Comito T, Tozzi A, Navarria P, Fogliata A, Clerici E, et al. Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. J Cancer Res Clin Oncol. 2015;141(3):543-53.
116. Van den Begin R, Engels B, Gevaert T, Duchateau M, Tournel K, Verellen D, et al. Impact of inadequate respiratory motion management in SBRT for oligometastatic colorectal cancer. Radiother Oncol. 2014;113(2):235-9.
117. van Laarhoven HW, Kaanders JH, Lok J, Peeters WJ, Rijken PF, Wiering B, et al. Hypoxia in relation to vasculature and proliferation in liver metastases in patients with colorectal cancer. Int J Radiat Oncol Biol Phys. 2006;64(2):473-82.
118. Bae SH, Kim MS, Cho CK, Kang JK, Kang HJ, Kim YH, et al. High dose stereotactic body radiotherapy using three fractions for colorectal oligometastases. J Surg Oncol. 2012;106(2):138-43.
119. Qiu H, Katz AW, Chowdhry AK, Usuki KY, Singh DP, Metcalfe S, et al. Stereotactic Body Radiotherapy for Lung Metastases from Colorectal Cancer: Prognostic Factors for Disease Control and Survival. Am J Clin Oncol. 2018;41(1):53-8.
120. Kim MS, Yoo SY, Cho CK, Yoo HJ, Choi CW, Seo YS, et al. Stereotactic body radiation therapy using three fractions for isolated lung recurrence from colorectal cancer. Oncology. 2009;76(3):212-9.
121. Kang JK, Kim MS, Kim JH, Yoo SY, Cho CK, Yang KM, et al. Oligometastases confined one organ from colorectal cancer treated by SBRT. Clin Exp Metastasis. 2010;27(4):273-8.
122. Francolini G, Detti B, Ingrosso G, Desideri I, Becherini C, Carta G, et al. Stereotactic body radiation therapy (SBRT) on renal cell carcinoma, an overview of technical aspects, biological rationale and current literature. Crit Rev Oncol Hematol. 2018;131:24-9.
123. Wersall PJ, Blomgren H, Lax I, Kalkner KM, Linder C, Lundell G, et al. Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. Radiother Oncol. 2005;77(1):88-95.
124. Viani GA, Arruda CV, Hamamura AC, Faustino AC, Freitas Bendo Danelichen A, Guimaraes FS. Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Recurrence: A Meta-analysis. Am J Clin Oncol. 2019.
125. Grozman V, Onjukka E, Wersall P, Lax I, Tsakonas G, Nyren S, et al. Extending hypofractionated stereotactic body radiotherapy to tumours larger than 70cc - effects and side effects. Acta Oncol. 2021:1-12.
126. Grozman V, Onjukka E, Wersall P, Lax I, Tsakonas G, Nyren S, et al. Extending hypofractionated stereotactic body radiotherapy to tumours larger than 70cc - effects and side effects. Acta Oncol. 2021;60(3):305-11.
127. Bentzen SM, Gregoire V. Molecular imaging-based dose painting: a novel paradigm for radiation therapy prescription. Semin Radiat Oncol. 2011;21(2):101-10.
128. Tekatli H, van 't Hof S, Nossent EJ, Dahele M, Verbakel W, Slotman BJ, et al. Use of Stereotactic Ablative Radiotherapy (SABR) in Non-Small Cell Lung Cancer Measuring More Than 5 cm. J Thorac Oncol. 2017;12(6):974-82.
129. Peterson J, Niles C, Patel A, Boujaoude Z, Abouzgheib W, Goldsmith B, et al. Stereotactic Body Radiotherapy for Large (> 5 cm) Non-Small-Cell Lung Cancer. Clin Lung Cancer. 2017;18(4):396-400.
130. Verma V, Shostrom VK, Kumar SS, Zhen W, Hallemeier CL, Braunstein SE, et al. Multi-institutional experience of stereotactic body radiotherapy for large (>/=5 centimeters) non-small cell lung tumors. Cancer. 2017;123(4):688-96.

131. Woody NM, Stephans KL, Marwaha G, Djemil T, Videtic GM. Stereotactic Body Radiation Therapy for Non-Small Cell Lung Cancer Tumors Greater Than 5 cm: Safety and Efficacy. Int J Radiat Oncol Biol Phys. 2015;92(2):325-31.
132. Flohr T, Petersilka M, Henning A, Ulzheimer S, Ferda J, Schmidt B. Photon-counting CT review. Phys Med. 2020;79:126-36.