

# 1 Treatment Planning for Patients with multiple lung metastases

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## 1.1 Introduction

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Lung cancer is the leading cause of cancer-related death, with approximately 160 000 deaths in the U.S. in 2014 [Siegel et al., 2014]. More than half of all patients with lung cancer are diagnosed with stage IV non-small cell lung cancer (NSCLC) [Ramalingam and Belani, 2008, Iyengar et al., 2014]. Prognosis for stage IV NSCLC is poor, with only 12 months median survival after first line chemotherapy [Socinski et al., 2013].

Stereotactic body radiation treatment (SBRT) shows good results for treating NSCLC [Baumann et al., 2009, Fakiris et al., 2009, Grutters et al., 2010, Ricardi et al., 2010, Timmerman et al., Greco et al., 2011]. Furthermore, several studies have shown that SBRT can be used in the setting of limited metastatic disease [?, Salama et al., 2012, Iyengar et al., 2014]. Passive scattering particle therapy has also proved as an effective treatment for NSCLC [Grutters et al., 2010, Tsujii and Kamada, 2012] and it was shown in Chapter [?] that scanned carbon ions (PT) could also be used as a treatment modality for NSCLC. One of the conclusions of study in Chapter ?? was that patients with multiple metastases would especially benefit from PT compared to SBRT. However, limitations of this study were small number of patients (4) and single-field uniform optimization (SFUD) used in treatment planning. Since patients with multiple metastases can present complex geometry, intensity modulated particle therapy (IMPT) might provide better treatment plan than SFUD.

An investigation of IMPT with state of the art 4D optimization for treating lung cancer patients with multiple metastases was made. Treatment plans were generated with different 4D optimization techniques and compared with SBRT plans, which were actually used for treating patients.

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## 1.2 Materials and Methods

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For creation of treatment plans 4D extension of GSI's treatment planning system TRiP98 [Krämer and Scholz, 2000, Richter et al., 2013] was used and modified. A description of modifications and tools used will be given here, alongside with patient data and analysis description.

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### 1.2.1 Patient data

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In this study, 8 patients with 2 - 5 lung metastases summing to 24 metastases in total were included. The lesion size was  $4.2 \text{ cm}^3$  (median, 25-75% 2.4 – 22.2) and peak-to-peak motion was 5.9 mm (2.7 – 8.1). Details are given in Table 1.1. Target motion and PT treatment planning were based on a 4D-CT, consisting of 10 phases (0 - 9), with phase 0 (end-inhale) chosen as a reference phase. A registered positron emission tomography (PET) scan was used to delineate clinical target volumes (CTV).

Patients 1 - 4 had no OARs in CTV vicinity (closer than 10 mm) and patients 5 - 8 had at least one OAR in CTV vicinity (closer than 10 mm).

Patients were treated with SBRT at Chamaplimaud Center for the Unknown, Lisbon (Portugal), with different fraction schemes. Number of fractions and doses delivered are given in Table 1.1.

Table 1.1: Target characteristics, with CTV volumes, peak-to-peak motions, fractination schemes and number of fields used for treatment planning. Last column shows an OAR in target vicinity (closer than 10 mm). SA stands for smaller airways and esoph. for esophagus.

Patient	Target	Volume (cm <sup>3</sup> )	Peak-to-peak motion [mm]	Fractination scheme	Number of fields	OAR in proximity
1	a	10.2	3.4	1 x 24 Gy	2	SA
	b	14.4	2.8			
2	a	2.3	12	1 x 24 Gy 5 x 7 Gy	2	
	b	0.4	11.8			
3	a	3.8	5.8	1 x 24 Gy	2	
	b	4.3	0.8			
	c	2.7	3.4			
	d	3.1	2.1			
	e	0.5	0.5			
4	a	139	0.6	1 x 24 Gy	3	
	b	9.2	2.0			
5	a	4	9	3 x 9 Gy 1 x 24 Gy	5	SA, esoph.
	b	0.8	7.8			
6	a	3.4	5	1 x 24 Gy	3	Heart
	b	2.4	4.4			
	c	2.0	6.3			
	d	2.4	6.4			
7	a	20.6	7.4	1 x 24 Gy	4	SA
	b	27.1	6.0			
8	a	136	12	3 x 9 Gy 1 x 20 Gy 3 x 9 Gy 1 x 20 Gy 1 x 20 Gy	2	Heart
	b	12.4	2.5			
	c	123	14			
	d	80.7	17			Heart
	e	86.7	6.6			

### 1.2.2 Multiple targets

TRiP98 optimization works on minimizing residual of a nonlinear equation system [Krämer and Scholz, 2011]. The minimizing function  $E(N)$  for particle number  $\vec{N}$  goes as:

$$E(\vec{N}) = \sum_{i \in T} \left( D_{pre}^i - D_{act}^i(\vec{N}) \right) = \sum_{i \in T} \left( D_{pre}^i - \sum_{j=1}^n c_{ij} N_j \right) \quad (1.1)$$

For a CT voxel  $i$  in target  $T$ ,  $D_{pre}$  and  $D_{act}$  are the prescribed and the actual dose, respectively. The coefficient  $c_{ij}$  stands for correlation between dose deposition and field position  $j$  at a voxel

$i$ , with  $n$  the number of fields. There is no restriction for the number of targets or fields in the minimizing function, so it can be expanded to:

$$E(\vec{N}) = \sum_T \sum_{i \in T} \left( D_{pre}^i - \sum_{j=1}^n c_{ij} N_j \right) \quad (1.2)$$

However, the setup of raster points in TRiP98 allowed only one target. It was therefore expanded in a way that a field was designated to a specific target, as displayed in Fig 1.1. Raster points for each field are created only around designated target. Contribution from all fields are then calculated in optimization. When a field from one target contributes dose to the other target this is taken into account in optimization function, specifically in coefficient  $c_{ij}$  in Eq. 1.3. Because the optimization function was not changed, all TRiP98 4D functionalities could be used, as explained in next sections.

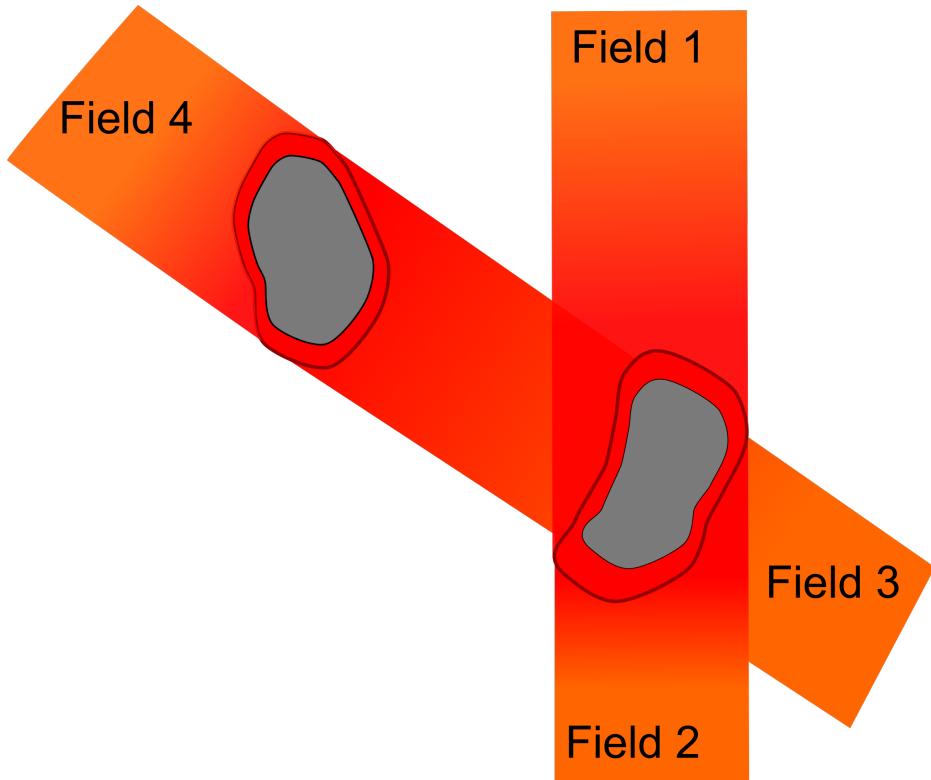


Figure 1.1: Multiple targets irradiation. Fields 1 and 2 are designated to target a and fields 3 and 4 to target b. Optimization takes into account all target voxels and contributions from all fields.

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### 1.2.3 Optimization techniques

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Investigation of two different optimization techniques to handle range changes in moving tumors was made. For each patient, two sets of plans were created: field-independent ITV (indITV) and 4D optimization (4Dopt).

- **Field-independet ITV:** A water-equivalent path length ITV (WEPL-ITV) is different for each field, creating unnecessary margins when combining WEPL-ITV from different fields (see Fig. 1.2a). Graeff et. al proposed a solution to include range margin into the field description itself, instead of creating a bigger PTV [Graeff et al., 2012]. Thus, no unnecessary margins are created. Treatment plans were made for all targets with intensity IMPT on a indITV in reference phase.
- **4D Optimization:** IMPT with indITV can produce inhomogeneous fields that yield homogeneous dose but only in reference phase. The WEPL can change in different motion phases, leading to inhomogeneous dose. 4Dopt uses WEPL-ITV for raster setup, however the actual optimization is performed on each target voxel in each motion state  $k$ . The optimization function thus changes to [Graeff et al., 2012]:

$$E(\vec{N}) = \sum_{T_k} \sum_{k=1}^m \sum_{i \in T_k} \left( D_{pre}^i - \sum_{j=1}^n c_{ijk} N_j \right) \quad (1.3)$$

All targets were treated with IMPT and 4D optimization. A subset of motion states 0, 50 and 70% was used for targets 7a -7d and 8b (see Table 1.1) due to large optimization problem - beside multiple targets, OAR was also included in motion states [Graeff et al., 2012].

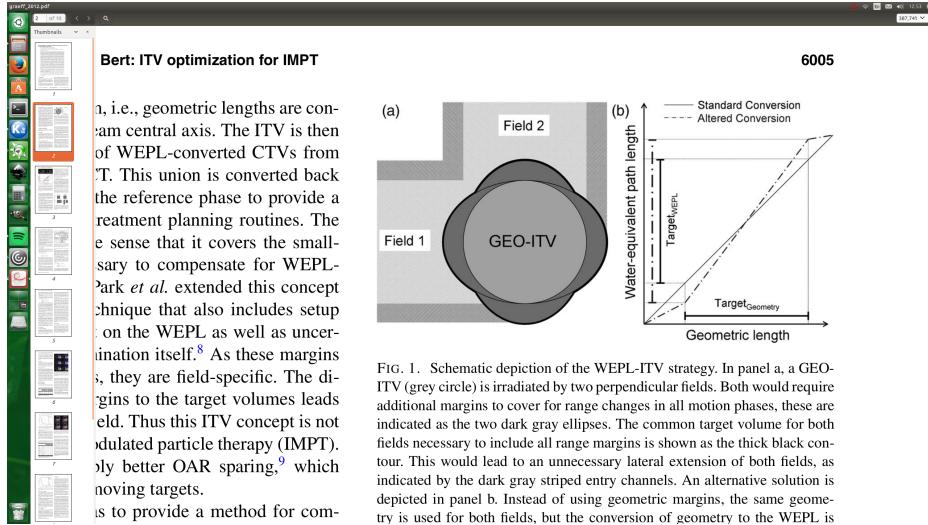


Figure 1.2: Schematic presentation of the indITV. (a) Dark gray ellipses show margins needed for specific fields to account for range changes in different motion states. When common target volume for two perpendicular fields is generated (this black contour) it creates unnecessary lateral extension of both fields, as shown by the dark gray entry channels. A solution is shown in (b). Rather than using standard, geometric, margins, both fields use the same geometry, however the conversion of geometry to WEPL is altered for each field. The plot in (b) shows the standard (solid line) and an altered conversion (dashed-dotted line) for a beam passing a homogeneous CTV. The altered conversion increases the WEPL extent and thus implicitly increasing margins for a single field only. Figure taken from [Graeff et al., 2012]

Finally, fields, resulting from the two optimization techniques mentioned, were used to calculate 4D doses. The same number of fields and the same field angles were used in both techniques.

#### 1.2.4 Treatment planning

An isotropic margin of 3 mm was added to each CTV to account for uncertainties in treatment delivery. An WEPL-ITV was constructed on the CTV with margins for each individual field, which was than used for optimization (SFUD and inITV) or for raster setup (4Dopt). SFUD and indITV plans were made on an end-inhale phase of a 4D-CT. Due to large memory demands, targets in each lung were optimized seperately.

The objective for target was 99% of each target volume should receive at least 100% of the planned dose ( $D_{99\%} \geq 100\%$ ). Furthermore, the doses to the OARs should be under the limits given by AAPM task group [Benedict et al., 2010]. Each plan after had to meet target and OAR objectives.

Afterwards 4D-dose was calculated for two motion periods (3.6 sec and 5.0 sec) and two starting phases ( $0^\circ$  and  $90^\circ$ ) as explained in Section ???. Motion was mitigated with five slice-by-slice rescans that were applied to each plan.

Detailed explanation of SBRT treatment planning is given in Section ??.

For patients 5 - 7 the dose limits to the OARs (stated in Table 1.1) could not be respected by including them in optimization. It was necessary to add margins to the OAR and then subtract OAR plus margins from the target. An algorithm was introduced into TRiP98 to automatically find the margins needed for an acceptable treatment plan.

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### 1.3 Results

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Example of different treatment plans for a single patient is shown in Fig. 1.3.

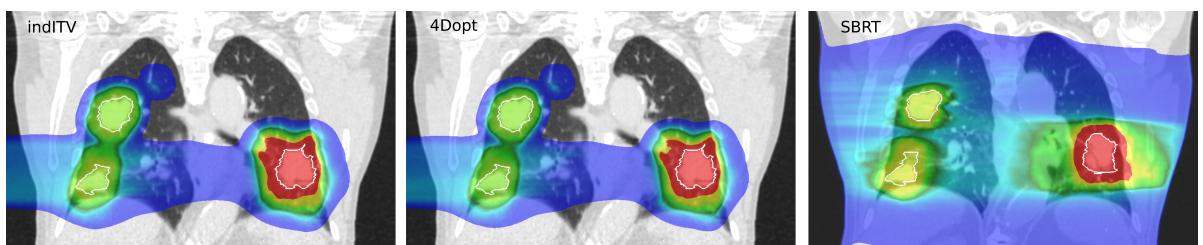


Figure 1.3: Treatment plans for indITV (left), 4Dopt (middle) and SBRT (right) for SBRT (solid lines) on a same patients. CTV contours are outlined in white.

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#### 1.3.1 Target Coverage

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Results for CTV  $D_{99\%}$  for all patients are shown in Table 1.2. All SBRT plans were approved by a physician, even though the prescription dose for patients 6 - 8 was not met due to an OAR proximity. Excluding patients 5 - 8, there were 8 cases of too low CTV dose across different motion types for indITV and 4Dopt, respectively, but not for the same targets. For patients 6 - 8 treatment plans with SFUD were clinically unacceptable, due to violation of OAR constraints. Both indITV and 4Dopt had higher CTV  $D_{99\%}$  than SBRT.

Range of CTV  $D_{99\%}$  across different motion types was 2, 1 and 2 Gy for SFUD, indITV and 4Dopt, respectively. **Statistical difference?**

Table 1.2: Target characteristics, with CTV volumes, peak-to-peak motions, fractination schemes and number of fields used for treatment planning.

Patient	Target	CTV $D_{99\%}$		
		indITV	4Dopt	SBRT
1	a	101.6(100.0 - 102.1)	101.0(101.0 - 101.0)	100.0
	b	101.6(101.0 - 102.1)	102.1(101.0 - 102.1)	100.0
1	a	100.9(100.9 - 101.9)	100.9(100.0 - 100.9)	105.6
	b	101.3(98.8 - 102.5)	102.5(100.0 - 102.5)	105.0
	c	101.4(100.0 - 101.9)	99.5(99.1 - 100.0)	106.5
	d	100.6(100.0 - 101.3)	98.8(98.8 - 101.3)	112.5
	e	102.5(100.0 - 102.5)	102.5(101.3 - 102.5)	101.3
1	a	101.0(100.0 - 101.0)	100.5(100.0 - 101.0)	101.0
	b	107.1(103.6 - 107.1)	100.0(100.0 - 103.6)	100.0
1	a	101.0(99.0 - 102.1)	99.0(99.0 - 102.1)	106.3
	b	102.1(99.0 - 102.1)	102.1(102.1 - 102.1)	103.1
	c	101.0(101.0 - 102.1)	101.6(101.0 - 102.1)	104.2
	d	102.1(99.0 - 102.1)	101.6(101.0 - 102.1)	107.3
	e	102.1(102.1 - 102.1)	102.1(101.0 - 102.1)	108.3
1	a	102.1(102.1 - 102.1)	102.1(102.1 - 102.1)	101.0
	b	99.0(99.0 - 99.0)	100.0(100.0 - 101.0)	102.1
1	a	84.3(82.4 - 85.2)	69.0(68.5 - 69.4)	66.7
	b	100.5(99.0 - 102.1)	100.5(99.0 - 102.1)	103.1
1	a	100.5(100.0 - 102.1)	99.5(99.0 - 101.0)	101.0
	b	100.5(100.0 - 101.0)	100.0(100.0 - 100.0)	101.0
	c	91.1(88.5 - 92.7)	92.7(86.5 - 93.8)	99.0
	d	97.4(93.8 - 100.0)	100.0(99.0 - 101.0)	94.8
1	a	87.5(86.5 - 89.6)	94.3(92.7 - 94.8)	69.8
	b	79.7(79.2 - 81.3)	78.6(77.1 - 79.2)	69.8

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### 1.3.2 Dose in OARs

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$D_{Max}$  and  $D_{Mean}$  for 8 OARs are shown in Table 1.3. There was significant difference between PT and SBRT in  $D_{Max}$  and  $D_{Mean}$  for heart, spinal cord, esophagus and aorta and in  $D_{Mean}$  for ipsilateral lung. No significant difference was observed for dose to OAR between different motion types or between indITV and 4Dopt.  $D_{Max}$  to all OARs was ? and for SBRT, indITV and 4Dopt, respectively.

DVHs for patients 6 - 8 are shown in Fig. **Do it!**. SA, Es were subtracted from for substracion from target were ..., compared to 2 mm in SBRT  $D_{Max}$  limit for smaller airways was exceeded for patients 6 and 8 in all cases. Heart  $D_{Max}$  limit was exceeded in 1 and 2 different motion cases for indITV and 4Dopt, respectively.

Table 1.3: Target characteristics, with CTV volumes, peak-to-peak motions, fractination schemes and number of fields used for treatment planning.

OAR	SFUD	indITV	4Dopt	SBRT
$D_{Max}$				
heart	12.4(0.0 - 39.3)	13.9(0.0 - 28.5)	14.6(0.0 - 29.3)	18.1(7.5 - 30.5)
spinalcord	0.4(0.0 - 8.0)	0.4(0.0 - 8.3)	0.3(0.0 - 8.5)	9.0(3.0 - 12.5)
smallerairways	16.0(0.0 - 26.0)	13.5(0.0 - 24.0)	13.8(0.0 - 25.0)	15.6(0.0 - 22.8)
esophagus	0.9(0.0 - 23.8)	0.6(0.0 - 23.5)	0.9(0.0 - 22.0)	11.5(5.5 - 25.5)
trachea	0.0(0.0 - 3.8)	0.0(0.0 - 1.3)	0.0(0.0 - 0.8)	0.4(0.0 - 7.5)
aorta	6.9(2.0 - 23.8)	4.6(0.0 - 28.5)	6.0(1.5 - 26.5)	18.1(6.3 - 31.0)
Ipsilateral lung	26.4(8.0 - 52.3)	27.0(0.0 - 34.8)	26.5(8.0 - 30.3)	26.4(10.0 - 32.3)
$D_{Threshold}$				
heart	3.4(0.0 - 10.0)	2.3(0.0 - 15.8)	3.0(0.0 - 13.5)	11.1(6.0 - 22.3)
spinalcord	2.0(0.0 - 32.0)	1.4(0.0 - 32.0)	3.3(0.0 - 32.0)	8.0(2.8 - 11.0)
smallerairways	0.0(0.0 - 23.0)	0.0(0.0 - 19.3)	0.0(0.0 - 20.5)	2.6(0.0 - 15.3)
esophagus	0.0(0.0 - 2.8)	0.0(0.0 - 3.0)	0.0(0.0 - 2.3)	6.5(3.3 - 11.8)
trachea	0.0(0.0 - 0.0)	0.0(0.0 - 32.0)	0.0(0.0 - 32.0)	1.7(0.0 - 32.0)
aorta	1.3(0.0 - 5.5)	1.1(0.0 - 11.8)	1.1(0.0 - 9.5)	10.6(4.0 - 23.0)
Ipsilateral lung	0.0(0.0 - 0.0)	0.0(0.0 - 0.0)	0.0(0.0 - 0.0)	0.0(0.0 - 6.1)

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## 1.4 Summary and Discussion

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Clinically valid SBRT plans have been compared to PT treatment plans for NSCLC patients with multiple metastases. To the best of our knowledge, this is the first study of treating multiple NSCLC metastases. Novel approach was used to handle multiple targets, together with state of the art 4D PT treatment planning. Furthermore, 4D doses were calculated for PT treatment plans. PT on average delivered less dose to OAR, while there were no significant difference in target coverage. The most apparent difference is in lung V<sub>20%</sub>, which was 3333% lower in PT, due to the narrow entry channel PT use.

Patients 1 - 5 did not require OAR implementation in optimization and nevertheless no OAR constraints were violated. Even though patient 2 and 4 had 5 metastases each. For patients 1 - 5 the OARs were at least 10 mm away from the CTV, whereas for patient 6 - 8 they were closer than 10 mm. The optimization problem was therefore more complex, especially in 4Dopt case. Patient 6 had the best target coverage with indITV, however  $D_{Max}$  for smaller airways was exceeded. For patient 7 PT and SBRT target coverage and heart  $D_{Max}$  were similar, but PT delivered less dose to other OAR. Patient 8 ?

### Comparison between 4dopt and inditv

Even though carbon-ions exhibit less dose to OAR with the same or even better target coverage, there is still room for improvement in PT treatment planning. An implementation of multi-criteria objective planning should bring even better dose distribution and allow physician to choose between trade-offs [Breedveld et al., 2007, Chen et al., 2010]. Additionally, multiple target optimization in PT would benefit from a shell around PT where dose would be minimized. Therefore excessive dose in healthy tissue would be further reduced. An introduction of a shell, however, would further enlarge the optimization problem, which is large already for complex geometry (patient 6 - 8). A solution for minimizing voxel number in optimization is currently being implemented by Prall et al **Citat, mogoce mal vec napisat.**

In Chapter ?? additional range margins could be used in treatment planning, because a single-field uniform dose (SFUD) optimization was done. Instead of defining margins in PTV, a solution was proposed to include uncertainties, such as range errors, in optimization process itself [Pflugfelder et al., 2008, Unkelbach et al., 2009, Fredriksson et al., 2011, Chen et al., 2012]. Chen et al. have shown it is possible to implement robust optimization in multi-criteria optimization as well.

Patient 7  $D_{Max}$  heart dose was over and under the limit across different motion types. This shows the necessity of making treatment plans robust against motion uncertainty, especially in the hypo-fractionated treatment. A recent treatment planning study by Liu et al. [Liu et al., 2016] showed a 4D robust optimization had better results than 3D robust optimization for NSCLC patients. However, only breathing starting phase was used as an uncertainty,

whereas different motion types should be considered. The disadvantage of 3D and 4D robust optimization is the enlargement of optimization problem.

Effect of motion on treatment plan delivery could be reduced by using gating. Gating, together with rescanning, has already been successfully implemented clinically for active beam scanning [Rossi, 2016, Mori et al., 2016] and it might be essential to use it in hypo-fractionated treatment of moving tumors.

A recent review showed good local control rates between 66 - 92% for patients treated with SBRT in reoccurred tumors in previous irradiation field [Amini et al., 2014]. However, there were grade 4 and 5 complications present, i.e. study by Trovo et al showed grade 5 pneumonia in 6% of patient treated [Trovo et al., 2014]. As shown in our study, PT delivers less dose to the OAR and could hence reduce the number of complications.

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## 1.5 Conclusions

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PT delivers less dose to OAR compared to SBRT in NSCLC patients with multiple disease sites, while maintaining the same target coverage. Caution has to be taken in patients with OAR in CTV vicinity (less than 10 mm), where doses to OAR differ across different motion types.

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