**In Silico Comparison of Photons versus Carbon Ions in Single Fraction Therapy of Lung Cancer**

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**Keywords: SDRT, particle therapy, lung cancer, motion mitigation, single fraction**

**Abstract**

**Purpose**

Single dose image guided radiation therapy (SDRT) shows good results for lung cancer treatment. Better normal tissue sparing might be achieved with scanned carbon ion therapy (CiT). Therefore an in silico trial was conducted to find potential advantages of and patients suited for CiT.

**Methods**

For 19 patients treated with SDRT, CiT plans were calculated on 4DCTs with simulated breathing motion. Prescribed target dose was 24 Gy in single fraction and OAR constraints used for photon planning were respected. Motion was mitigated by rescanning and range-adapted ITVs. Doses were compared to the original SDRT plans.

**Results**

CTV coverage was the same in SDRT and CiT. The field-specific PTV including range margins for CiT was 1.5 (median, 25-75% 1.3 – 2.1) times larger than for SDRT. Nevertheless, maximum point dose and mean dose in OAR were higher in SDRT by 2.5 (0.3– 4.8) Gy and 0.6 (0.2– 1.7) Gy, respectively. Patients with a CTV > 2.5 cc or with multiple lung lesions showed larger differences in OAR doses in favor of CiT.

**Conclusions**

Patients receive less dose in critical OARs such as heart, spinal cord, esophagus, trachea and aorta with CiT, while maintaining the same target coverage. Patients with multiple or larger lesions are particularly suited for CiT.

**Keywords: SDRT, particle therapy, non-small-cell lung cancer, motion mitigation**

# Introduction

Lung cancer is one of the leading medical problems worldwide with approximately 1.4 million deaths per year [1]. Surgery is usually the first choice in treating localized non-small cell lung cancer (NSCLC). However, in recent years stereotactic body-radiation therapy with photons (SBRT) showed very promising results, with high local control-rates of NSCLC [2-7].

Scanned particle therapy (PT) can produce sharp dose gradients with a finite range of the beam and can thus provide higher healthy tissue sparing. This reduces both side effects as well as the risk of secondary cancer [8]. Treatment of lung tumors with PT is still challenging due to interplay and radiological path length changes [9]. The latter can be substantial when dense tissue (e.g. the solid tumor mass) is replaced with low-density tissue (lung) due to motion.

Nevertheless, in recent years there have been several clinical studies using PT on lung tumors with promising results [10]. It is important to note that all of these studies used passive beam scattering avoiding the problem of interplay between organ motion and scanning beam motion. On the other hand, active beam scanning can provide even better dose shaping which becomes even more important in high dose single fractionation regimes. Therefore an in silico study comparing photon and active scanning particle therapy for NSCLC is necessary before clinical implementation.

Even though protons are most commonly used in PT [11],good clinical experience is available also for carbon ion therapy [12]. We hypothesize that

1. active scanning with carbon ions (CiT) could provide better healthy tissue sparing than photons in treating lung tumors or metastases due to its favorable dose profile.
2. patient characteristics can be identified that allow the selection of patients especially suited for CiT.

To evaluate our hypothesis, an in silico comparison of simulated CiT plans to single dose SBRT (SDRT) plans actually delivered was conducted. Target coverage and a wide range of OAR doses were assessed both with and without simulated motion on 4DCTs.

# Methods

## Patient data

Our study included 19 patients with in total 26 lesions that were actually treated with SDRT at the Institute. The lesion size was 2.9 cc (median, 25-75% 1.4 – 9.7) and peak-to-peak motion was 3.1 mm (1.6 – 5.6). Three patients had two targets, one had five and the rest one. 13 lesions were right-sided, 12 were left-sided and one was located in right cardiophrenic space. An overview of tumor characteristics can be found in Table 1.

Two computed tomographies (CT) were available for all patients. A planning CT was used for OAR delineation and SDRT planning. Target motion was estimated on a second, time-resolved CT (4D-CT), consisting of 10 phases (0% - 90%). Clinical target volumes (CTV) were delineated using a registered positron emission tomography (PET) scan.

The planning objectives were that 99 % of planning target volume (PTV) must receive at least 24 Gy (V99% ≥ 24 Gy) in a single fraction, while all OAR constraints as defined in the AAPM task group 101 report on stereotactic radiotherapy had to be respected [13].

Table - Patient characteristics showing lesion locations, stages, peak-to-peak motions, and volumes of corresponding CTV, SPTV and FTV.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **Volume (cc)** | | |
| **Patient** | **Lesion number** | **Lesion location** | **Stage** | **peak-to-peak motion (mm)** | **CTV** | **SPTV** | **FTV** |
| 1 | 1 | LSL | IIa | 4.8 | 35.9 | 100.0 | 179.0 |
| 2 | 2 | LSL | Ia | 3.1 | 1.6 | 7.7 | 40.6 |
| 3 | 3 | IRL | IV | 12.0 | 2.3 | 11.6 | 32.0 |
| 4 | 4 | RSL | Ia | 0.5 | 6.9 | 25.2 | 38.0 |
| 5 | 5 | ILL | IV | 4.4 | 2.5 | 15.0 | 20.5 |
| 6 | 6 | ILL | IV | 7.5 | 1.4 | 7.7 | 26.5 |
| 7 | 7 | RSL | IV | 3.9 | 16.0 | 40.0 | 72.5 |
| 8 | 8 | ILL | IV | 0.6 | 139.0 | 261.0 | 255.0 |
| 8 | 9 | LSL | IV | 2.0 | 9.2 | 35.0 | 46.5 |
| 9 | 10 | IRL | IV | 3.4 | 10.2 | 38.0 | 45.5 |
| 9 | 11 | ILL | IV | 2.8 | 14.4 | 46.4 | 57.2 |
| 10 | 12 | ILL | IV | 5.8 | 3.8 | 17.4 | 23.4 |
| 10 | 13 | RSL | IV | 0.8 | 4.3 | 17.7 | 26.3 |
| 10 | 14 | LSL | IV | 3.4 | 2.7 | 14.5 | 23.1 |
| 10 | 15 | RSL | IV | 2.1 | 3.1 | 15.4 | 33.5 |
| 10 | 16 | LSL | IV | 0.5 | 0.5 | 5.4 | 6.7 |
| 11 | 17 | ILL | IV | 7.8 | 0.8 | 6.1 | 23.5 |
| 12 | 18 | LSL | IV | 0.1 | 1.7 | 15.0 | 23.5 |
| 13 | 19 | IRL | IIIb | 11.4 | 27.0 | 137.0 | 118.5 |
| 14 | 20 | RSL | Ia | 2.2 | 1.7 | 10.0 | 23.4 |
| 15 | 21 | RSL | IV | 0.2 | 0.9 | 3.2 | 14.9 |
| 16 | 22 | RSL | IV | 2.2 | 3.9 | 22.1 | 27.5 |
| 17 | 23 | LSL | IV | 3.1 | 9.8 | 28.0 | 51.0 |
| 18 | 24 | RSL | IV | 8.1 | 0.6 | 3.3 | 4.1 |
| 19 | 25 | LSL | IV | 1.4 | 0.8 | 5.9 | 10.0 |
| cc, cubic centimeters; RSL, right superior lung; IRL, inferior right lung; LSL, left superior lung; ILL, inferior left lung; CTV, clinical target volume; SPTV, SDRT planning target volume; FTV, field-specific target volume; | | | | | | | |

## Definition of target volume

To account for range changes relevant for particles only, different PTV definitions were used for SDRT and CiT, as shown in Figure 1. Within this paper they will be named SPTV and FTV (field-specific target volume) for SDRT and CiT, respectively.

In SDRT, the responsible clinician determined the maximum breathing motion of the CTV from the 4D-CT, hence creating an ITV. This ITV plus an additional 3 mm for setup uncertainty yielded the SPTV.

FTV was constructed following principles from Graeff et al [14]. Each beam has a unique FTV. For setup uncertainty margins of 3 mm laterally and 1 mm in beam’s eyes view (BEV) were used on the CTV. Afterwards a water-equivalent path length ITV (WEPL-ITV) was build, using transformation maps from the B-Spline deformable registration of the 4D-CT data [15]. Additional 2 mm + 2 % proximal and distal margins were added in BEV to account for uncertainty from Hounsfield units to water equivalent path length conversion.

If the target overlapped with an OAR (e.g. small airways) then OAR plus a margin of 2-5 mm was subtracted from SPTV or FTV.

## SDRT Treatment Planning

The clinical plans were calculated with the Eclipse v10 planning system (Varian Medical Systems, Palo Alto, Ca) using the AAA algorithm. All plans delivered 24 (7 for one metastasis) Gy, generally using 4 VMAT partial arcs. For tumor sizes > 2.5 cm a calculation grid of 2.5 mm was used, otherwise this was 1 mm. During optimization, a first iteration included the SPTV only, after which the OARs were added. In order to lower OAR dose and improve the SPTV homogeneity, we created an artificial shell of 2 cm around the SPTV and minimized the dose there as well. Finally, an intermediate dose calculation with AAA was mandatory to get an adequate SPTV coverage after optimization.

## Carbon Ions Treatment Planning

For CiT, state of the art 4D treatment planning software TRiP98 was used [16]. A single field uniform dose plan (SFUD) was optimized on the FTV in the end-inhale reference phase of the 4D-CT. Dose was then calculated on end-inhale (3D-0%) and end-exhale (3D-50%) phases. 4D dose delivery was simulated over the whole breathing cycle with two different breathing periods (3.6 and 5 s) and two different starting phases (0° and 90°). Simulations without motion compensation (interplay) and with slice-by-slice rescanning were performed. Five rescans were used for the majority of targets (*n*=24), whereas 20 rescans were used for targets (*n*=2) where the interplay effects were too big to achieve a satisfactory target coverage.

Dose was computed considering the relative biological effectiveness (RBE) following the local effect model (LEM) IV [17]. For a conservative estimation an alpha beta ratio of 10 Gy and 2 Gy were used for target and OARs, respectively. This led to RBE of approximately 1.1 in target tissue and approximately 1.1 to 3 in OARs.

Most targets (*n*=20) were planned with two fields. For remaining targets, one (*n=1*)*,* three (*n*=3) or four (*n*=2) fields were used due to proximity of OARs. A beam spot spacing of 2 mm, a focal size of approximately 6 mm (FWHM), a 3 mm ripple filter and in most cases a bolus of 80 mm width were used.

## Dose metrics and analysis

For comparison between SDRT and CiT the following dose metrics were used – relative volume of the CTV receiving 100 % of prescribed dose (V100%), the minimum dose in 95% of the volume (D95%), the maximum point dose (DMax), and the mean dose (DMean). The first two metrics, V100% and D95% were used to compare target coverage, whereas OAR dose was compared with DMax and DMean.

For 4D CiT dose calculations, mean and standard deviation were calculated between different breathing periods and starting phases.

Paired t-tests were performed to compare the dose metrics and for post-hoc exploratory analysis between groups a two-sided t-test with Welch correction for different variances was carried out. A p-value < 0.05 was considered significant. Dose differences are always reported such that higher dose levels for SDRT result in positive values.

# Results

Examples of two SDRT and 4D-rescan CiT treatment plans are shown in Figure 2. Patient A has two lesions in close proximity to the spinal cord. Patient B has a small lesion (0.87 cc) in the superior position of the left lung wing. V24Gy is 100 % for SDRT and CiT in all CTVs for Patient A and B; average OAR difference between SDRT and CiT in DMax is 5.3 Gy and 1.5 Gy and in mean dose 1.2 Gy and 0.6 Gy, respectively for patient A and B.

## Target Coverage

Difference in PTV definition resulted in 1.5 (1.3 – 2.1) times bigger FTV than SPTV. There was no significant difference in CTV D95% between SBRT and any CiT calculation. For CTV V100% there was a significant difference between SDRT and 4D-interplay, 3.8 (0 – 6.1) % and no significant difference between SDRT and 3D-0%, 3D-50% or 4D-rescan.

Difference in V100% between 4D-rescan and 4D-interplay with respect to CTV peak-to-peak motion and average CTV range change in water is plotted in Figure 3. Range change was a better predictor of the V100% difference than geometric motion (r=0.75 vs. r=0.48).

There was a significant difference in V24Gy standard deviation between 4D-interplay and 4D-rescans, 1.8 (0 – 2.9) %, i.e. interplay simulation showed a larger variability in dose coverage in addition to the difference in averages.

## Dose in OARs

There was no significant difference in dose to OAR between the different CiT dose calculations. The dose metrics for SDRT and 4D-rescan CiT for OARs heart, spinal cord, smaller airway esophagus, trachea, aorta, ipsi- and contralateral lung are presented in Table 2. In almost all patients CiT deposited less dose in all OARs, except ipsilateral lung, where there was no statistical significant difference between SDRT and CiT.

The average OAR difference between SDRT and CiT was significant, 2.5 (0.3– 4.8) Gy for DMax and 0.6 (0.2– 1.7) Gy for DMean.

The contralateral lung did not receive any dose in 12 (71 %) patients with CiT.

Table Dose metrics for OARs. First value at each organ is from SDRT and the second from 4D-rescan. All values are shown as median and 25-75% in brackets.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **OAR** | **DMax (Gy)** | | **DMean (Gy)** | |
|  | Photon | Carbon | Photon | Carbon |
| Heart | 6.0 (0.3 – 11.6) | 0 (0 – 7.3) | 1.3 (0.1 – 2.2) | 0 (0 – 0.2) |
| Spinal Cord | 5.5 (3.3 – 8.5) | 0 (0 – 0) | 0 (0 – 0.3) | 0 (0 – 0) |
| Smaller Airways | 13.0 (9.8 – 17.1) | 11.0 (1.1 – 16.3) | 2.8 (1.5 – 5.8) | 0.7 (0 – 1.9) |
| Esophagus | 8.0 (3.9 – 8.4) | 0 (0 – 0.3) | 1.1 (0.6 – 1.5) | 0 (0 – 0) |
| Trachea | 4.3 (2.5 – 6.0) | 0 (0 – 0) | 1 (0.5 – 1.5) | 0 (0 – 0) |
| Aorta | 8.0 (5.1 – 21.9) | 1.0 (0 – 16.8) | 1.4 (0.7 – 1.6) | 0 (0 – 0.1) |
| Ipsilateral Lung | 26.3 (26.0 – 26.5) | 26.3 (25.8 – 26.8) | 2.3 (1.5 – 3.1) | 2.5 (1.6 – 3.4) |
| Contralateral Lung | 4.8 (3.5 – 6.8) | 0 (0 – 0.3) | 0.4 (0.2 – 0.6) | 0 (0 – 0) |

## Dependence on CTV Size

Significant differences were observed between patients with a single CTV smaller (*n=8)* or larger (*n=7)* than 2.5 cc for DMax and DMean, see Figure 4. For patients with a smaller CTV, the dosimetric advantage over SDRT was on average 1.3 Gy and 0.5 Gy lower for DMax and DMean, respectively. This was associated with FTV definition - the average volume ratio between FTV and SPTV was 2.9 (1.6 – 4.0) and 1.5 (1.3 – 1.8), for patients with CTV < 2.5 cc and CTV > 2.5 cc, respectively

Patients with multiple lesions were excluded in this comparison. The DMax and DMean difference were on average higher in these patients, but the number of patients was too low for statistical analysis.

# Discussion

This is the first in silico trial directly comparing clinically valid SDRT (or SBRT) plans to scanned carbon ion plans using state of the art 4D dose calculation and motion mitigation methods for NSCLC patients. Our study found that CiT deposited less dose to OARs compared to SDRT. Therefore CiT might be considered as an alternative treatment option to SDRT. The finite range of the beam permits a small number of fields and thus a narrow entry channel, so that critical OARs such as spinal cord, heart, esophagus, and the contralateral lung could be effectively spared using CiT, with typically low or even zero dose. CiT could be thus highly beneficial to patients with impaired contralateral lung function, because CiT deposited no dose in the contralateral lung in 11 patients, while SDRT irradiated the contralateral lung in all patients. Being an intensity-modulated arc therapy, SDRT had an advantage in some patients where the smaller airways were in a close proximity to CTV; SDRT could shape the dose distribution to reduce dose to the smaller airways, compensating CiT’s advantageous physical dose characteristics.

Further increase in OAR sparing could be achieved by using intensity modulated particle therapy (IMPT) instead of SFUD. While IMPT could lead to less dose in the OARs, it would make the plans less robust against the setup errors due to additional dose gradients between the fields. These gradients can be controlled by employing robust optimization to account for range, motion and setup uncertainties, which we will implement in a future 4D treatment planning study [18].

## Range Margins and Motion Mitigation

Since conventional geometric margins are not suitable for PT [19], margins based on range changes were used. Another trial comparing photon to proton therapy in NSCLC patients also used different PTV definitions to incorporate range changes [20]. As shown in our study, inclusion of range changes leads to increase in FTV, up to 4.7 times compared to SPTV. Furthermore, the difference between PTVs is bigger for smaller tumor sizes. Patients with bigger tumor volumes (CTV > 2.5 cc) are therefore better suited for treatment with CiT.

Our results confirm previously published results that interplay can lead to a dose degradation in treating moving targets with active scanned beam [21]. Figure 3 shows the importance of using 4D dose calculation and motion mitigation techniques in treating moving targets. Even small motions and/or range changes can lead to underdosage in CTV. While FTV appears a strong motion mitigation technique (no difference in CTV D95% between SDRT and CiT), it is necessary to use rescanning as well to get sufficient target coverage (CTV V100% = 100%). Rescanning is also more robust to different breathing periods and starting phases compared to 4D-interplay, indicated by the lower variance in the dose coverage metrics. Recent studies suggest that some patients require phase-controlled layer or volumetric rescanning for sufficiently robust target coverage [22,23]. The advantage of slice-by-slice rescanning is that no motion monitoring or assumptions on the breathing frequency are necessary.

## Clinical results

Grutters et al. have performed a meta-analysis on comparison between photon, proton and carbon ions in treating NSCLC [4]. They found similar 5-year survival rates for SBRT, protons and carbon-ions (around 40 %). However, the number of patients treated with particle therapy was low and they advise caution when interpreting the data. Also different fractionation schemes were used in the comparison. A more recent review was published by Tsujii and Kamada [10] where they reported a high 3-year survival rate for single-fraction carbon-ions (76.9 %). In comparison, SBRT had 55.8 % 3-year survival rate [6]. Additionally, no late treatment-related adverse effects were reported for carbon-ions, whereas in SBRT grade 3 was observed in up to 28 % of patients [2]. All patient data for PT was based only on passively scattered beam, but first patients are treated in thoracic and abdominal regions with an active beam scanning at the National Institute for Radiological Sciences (NIRS) in Japan [22].

## RBE and Proton Therapy

Carbon ions exhibit a radiobiological advantage, especially in the Bragg peak region. However, for high doses as used here the effect of RBE is not well documented and is subject to ongoing research [24]. For these high doses RBE for carbon ions should approach a value between 1 and 2 [25], which is in agreement with values in our study ( ~ 1.1).

Coincidently, RBE values in the target at high doses are similar to those used clinically in proton therapy. Our results are in agreement with several in silico studies comparing SBRT and proton therapy for NSCLC [20,26,27]. Furthermore, a study made by Kadoya reached the same conclusion as our study, that patient with larger CTV and/or multiple CTVs would benefit more from proton therapy [26]. A recent phase II trial for patients with multiple sites of extracranial disease showed very good results for photons [28]. Based on our conclusions proton and/or carbon-ion therapy is a sensible treatment option. Carbon-ions shows considerably lower lateral scattering though, which should result in even better OAR sparing than protons.

## Study limitations

The 4D dose calculations were based on a regular breathing pattern, which typically varies during patient treatment and/or between 4DCT acquisition and actual treatment [29,30]. A possible solution was proposed by Boye et al. to get motion information from 4D magnetic resonance imaging (4DMRI) and use it in 4D dose calculations [31].

Furthermore, SDRT treatment plans were done on a static case in contrast to a 4D dose calculation done for CiT. This should not influence the results of our study, since motion has a smaller impact on photon dose distributions [32], whereas it is imperative in CiT dose calculations [9].

There were also differences in treatment planning. CiT plans were done by a single person in a research setting, whereas SDRT plans were made by different people under clinical conditions with the requirement to finish the plans on time.

Slight changes also existed between the planning CT, used for SDRT treatment plans and 4D-CT used for CiT treatment plans, even though 4D-CT was usually acquired right after the planning CT. The propagation of contours from the planning CT to the 4D-CT and also for the 4D dose calculation rely on deformable image registration (DIR), where even small changes can effect 4D dose distribution [33]. Results from deformable registration were therefore thoroughly checked with different approaches, such as inspection of the warped image, evaluation of the Jacobian values and the inverse consistency of the vector field. However, the transformation of the dose with DIR is a debated topic and might jeopardize the simulated results, especially with respect to the 4D target coverage. On the other hand, dose differences in OARs were large and should be robust against vector field errors in the order a few mm. Nevertheless, further studies are warranted, possibly using advanced moving phantoms for an experimental validation [34], and finally also clinical trials.

## Application

Scanned carbon ion therapy is available only in a limited number of clinics, mainly due to the considerably higher cost in comparison to photon linacs. Therefore a careful patient selection appears sensible. Patients with larger and multiple lesions where SDRT might be limited due to OAR constraints could be referred to carbon centers. In this study, already lesions larger than 2.5 cc were found to benefit significantly stronger from CiT.

# Conclusion

SDRT and CiT both achieved satisfactory target dose. In most patients CiT deposited less dose in all OARs (including heart, spinal cord, esophagus, trachea and aorta). Patients with multiple lesions and/or with large target volumes might be preferentially selected for particle therapy.

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