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Proton therapy

Photons, protons or carbon ions for stage I non-small cell lung cancer – Results of the multicentric ROCOCO *in silico* study

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ABSTRACT

Purpose: To compare dose to organs at risk (OARs) and dose-escalation possibility for 24 stage I non-small cell lung cancer (NSCLC) patients in a ROCOCO (Radiation Oncology Collaborative Comparison) trial.
Methods: For each patient, 3 photon plans [Intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and CyberKnife], a double scattered proton (DSP) and an intensity-modulated carbon-ion (IMIT) therapy plan were created. Dose prescription was 60 Gy (equivalent) in 8 fractions.
Results: The mean dose and dose to 2% of the clinical target volume (CTV) were lower for protons and ions compared with IMRT ($p < 0.01$). Doses to the lungs, heart, and mediastinal structures were lowest with IMIT ($p < 0.01$), doses to the spinal cord were lowest with DSP ($p < 0.01$). VMAT and CyberKnife allowed for reduced doses to most OARs compared with IMRT. Dose escalation was possible for 8 patients. Generally, the mediastinum was the primary dose-limiting organ.
Conclusion: On average, the doses to the OARs were lowest using particles, with more homogenous CTV doses. Given the ability of VMAT and CyberKnife to limit doses to OARs compared with IMRT, the additional benefit of particles may only be clinically relevant in selected patients and thus should be carefully weighed for every individual patient.
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Introduction

The introduction of stereotactic body radiation therapy (SBRT) has led to an increase in radiotherapy use in early stage non-small cell lung cancer (NSCLC) patients and fewer untreated patients, which has driven up population-based survival for lung cancer [1]. SBRT is a form of high-precision radiotherapy, using large (ablative) radiation doses per fraction, generally in one to eight fractions over one to three weeks. A Biologically Effective Dose (BED) of more than 100 Gy has allowed for high local tumor control rates (>90%), comparable to those obtained with surgery, supporting its consideration in operable patients [2–4]. A pooled meta-analysis of the STARS and ROSEL trials has indicated non-inferiority of SBRT compared to surgery with respect to survival and disease progression, albeit in a small patient population with limited follow up. Furthermore, treatment related toxicity was generally low and found to be favorable compared to surgery, even though damage to central structures and the chest wall have been reported [4,5]. The photon-based SBRT techniques have evolved over the years from 3-dimensional (3D) conformal photon radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT), and volumetric modulated arc therapy (VMAT).

In recent years, there has been a massive expansion in particle therapy centers (mainly proton therapy) in clinical operation. Charged particles are characterized by the presence of the so-called 'Bragg peak', *i.e.*, dose deposition at an energy-dependent tissue depth, and a sharp dose falloff at the distal edge with no further dose deposition. Some centers use particles for (stereotactic) treatment of lung cancer and report outcomes seemingly comparable to photon radiotherapy despite the known difficulties with the delivery of particle beams to a moving tumor in the lung (e.g., range uncertainties, interplay effect) [6,7]. Several

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dosimetric studies on particles have shown a significant reduction in dose to surrounding organs at risk (OAR) and thus short- and long-term toxicities [8–12].

While there are multiple options for delivery of photon- or particle-based radiation therapy in early stage lung cancer patients, it is currently not known which technique is best in terms of target coverage and low dose to OARs. A randomized controlled trial comparing these techniques would require a very large patient cohort to show significant differences in local control and/or toxicity and likely be fraught with accrual difficulties. Hence, the multicenter international Radiation Oncology Collaborative Comparison (ROCOCO) was initiated in 2007 conducting several comparative *in silico* trials in multiple primary tumor sites, including lung cancer [8,13].

In this study on twenty-five patients with stage I NSCLC, we compared the doses to the OARs and the dose escalation probability for one SBRT fractionation schedule using five contemporary radiotherapy techniques with either photons (IMRT, VMAT and CyberKnife), double scattered protons (DSP) or intensity-modulated carbon ions (IMIT).

Patients and methods

Patients

Twenty-five consecutive patients with stage I NSCLC who underwent SBRT at MAASTRO clinic (Department of Radiotherapy, Maastricht University Medical Center+, The Netherlands) between February 2011 and June 2013 were included in this *in silico* planning study. The maximum tumor diameter was 3 cm and all tumors were at least 2 cm separated from the mediastinal structures and bronchial tree [14]. Most tumors were located peripherally, with 15 tumors (or their planning target volume; PTV) overlapping chest wall and ribs. This retrospective *in silico* planning study was approved by the Institutional Review Board of MAASTRO clinic.

Target and OAR definitions

Delineation of the target volumes and OARs was performed at MAASTRO clinic according to institutional guidelines. The OARs, gross tumor volume (GTV), clinical target volume (CTV) and PTV were delineated in the mid-ventilation phase of a four-dimensional-18F fluorodeoxyglucose positron emission tomography-computed tomography (4D-FDG-PET-CT) scan. For this purely dosimetric comparison between the modalities, a gated treatment was assumed without the use of an internal target volume (ITV) accounting for breathing motion. The following dose limiting OARs were delineated: the mediastinum (consisting of heart, great vessels, trachea, main bronchi and esophagus), lungs, esophagus, spinal cord and brachial plexus. The 'mediastinum' was expanded 5 mm to create a planning risk volume (PRV mediastinal envelope) to account for setup inaccuracy or movement. The ribs were contoured within 5 cm of the PTV (excluding the intercostal space; [15]). The chest wall constituted of a 1.5-cm expansion from the lungs. For comparison of the total lung dose, the GTV was subtracted from the total lung volume.

Treatment planning

For each patient, three photon plans (IMRT, VMAT and Cyberknife), a DSP plan and an IMIT plan were calculated at Catherina Hospital Eindhoven (CHE; the Netherlands), MAASTRO clinic, the Centre Hospitalier Universitaire de Liège (CHU; Belgium), the Hospital of the University of Pennsylvania (UPENN; USA), and the University Hospital of Marburg (UHM; Germany), respectively.

Irrespective of the clinically used dose, the prescribed dose was 60 Gy in 8 fractions, achieving a Biologically Effective Dose (BED) of 105 Gy, roughly equivalent to 87.5 Gy in 2 Gy fractions (EQD_2). Each center used its in house, clinically commissioned treatment planning system (TPS) assuring state-of-the-art dose calculations. Planning objectives were in accordance with several multi-institutional trials (e.g., RTOG 0618 and RTOG 0236), where 95% of the PTV should receive at least 100% of the prescribed dose, and the maximum dose (D_{max}) was not to exceed 140%. The dose was prescribed to the given PTV by all centers except for UPENN, which employed individualized uncertainty margins for DSP. According to the study protocol, the dose to the CTV was eventually evaluated. In order to guarantee uniform CTV dose level enabling comparison of the dose to the surrounding OARs, all plans were rescaled such that 99% of the CTV received 60 Gy (RBE equivalent).

For the OARs, consensus constraints were defined *a priori* among investigators from all centers prior to planning and largely mirrored 8-fraction radiotherapy institutional constraints: spinal cord, $\leq$32 Gy to 0.03 cm^3; esophagus and PRV mediastinal envelope, $\leq$41 Gy to 0.03 cm^3; heart, $\leq$46 Gy to 0.03 cm^3; volume of 'healthy' lungs (total lungs minus GTV) V_{20Gy} <15%; brachial plexus, $\leq$38 Gy to 0.03 cm^3 (delineated only for case where the caudal border of the brachial plexus was within 5 cm of the PTV); and cardiac device (if present) D_{max} = 2 Gy. Planning objectives for the thoracic wall included: ribs: $V_{32.5Gy}$ <1 cm^3 and D_{max} = 35 Gy; chest wall: $V_{32.5Gy}$ <30 cm^3 and D_{max} = 40 Gy. The following priorities were set for the objectives (numbered in order of decreasing importance): 1 = spinal cord, 2 = brachial plexus, 3 = lungs, 4 = PRV mediastinal envelope, 5 = ribs, 6 = chest wall, 7 = esophagus, and 8 = heart.

Photons

The step-and-shoot IMRT plans were calculated using Pinnacle v. 9.6 (Philips Radiation Oncology Systems, Fitchburg, WI). Five to seven (mainly equispaced) 6MV photon beams were employed, avoiding beam entrance through the contralateral lung. The VMAT plans were created using Eclipse v. 11.0 (Varian Medical Systems, Palo Alto, CA). The plans generally consisted of two 180 degree arcs with an energy of 10MV. CyberKnife plans were created using Multiplan v. 5.2.1 (Accuray Inc., Sunnyvale, CA). The non-coplanar beam arrangement was chosen from a large set of predefined nodes (full-path). A maximum of three collimators were used and the collimator diameter was case dependent (usually ranging from 60 to 80% of the largest PTV diameter).

Protons

In the DSP plans, the relative biological effectiveness (RBE) doses were calculated using an RBE of 1.1 for protons using Eclipse v. 11.0 (Varian Medical Systems). The field size was limited to 12 cm. Beam arrangements were chosen based on the path of least variation. PTV margins were determined by range * 3.5% plus 3 mm. Portals were designed to avoid OARs distal to the target. Plans used 2–3 fields as a tradeoff between treatment time and target conformity.

Carbon ions

The IMIT plans were calculated at the UHM using Syngo PT Planning (Siemens Health Care Systems, Erlangen, Germany), typically using 3 or 4 fields with a patient-specific beam arrangement assuming the use of a gantry. The RBE was calculated using the first version of the Local Effect Model (LEM1). The following spot scanning parameters were employed: a nominal spot size of 8 mm, a scanning grid and energy step size of 3 mm. The base data (e.g., energy range) used for planning was representative of facilities such as the ion-beam therapy centers in Heidelberg and Marburg.

Data storage and analysis

The Multicentric *In Silico* Trials In Radiotherapy (MISTIR) framework (http://www.mistir.info) was used for data storage and exchange. The datasets were downloaded from the MISTIR database by the participating ROCOCO partners to perform treatment planning. After completion of the treatment plans, the dose matrices were re-uploaded to the database in DICOM format (Digital Imaging and Communication in Medicine). The dose-volume metrics were extracted and compared to the IMRT plans, which was considered as the 'gold standard.' The following parameters were compared for CTVs: mean dose (D_{mean}); highest dose to 2% of the volume ($D_{2\%}$, near maximum dose), lowest dose to 98% of the volume ($D_{98\%}$, near minimum dose); and OARs: minimum dose to the 'hottest' 0.03 cm^3 ($D_{0.03cc}$, near maximum dose), V_{5Gy} and V_{20Gy}. To quantitatively assess the differences in conformity between the five modalities, conformation numbers (CN) were calculated for the CTV. The CN calculations where based on the formula described by van 't Riet et al. [8,16], rewritten as follows: $CN_{x\%} = (CTV_{x\%}/CTV) * (CTV_{x\%}/V_{x\%})$, where $CTV_{x\%}$ and $V_{x\%}$ represent the volume of the CTV or the overall volume, respectively, receiving a percentage (x%) of the prescribed dose. The CNs were calculated for x = 50%, 80% and 95%.

The dose escalation probability was assessed for each patient by upscaling the plans until reaching the constraint of any of the OARs, thereby reaching the maximum tolerated dose (MTD). Dose escalation was performed only if there was room for escalation for all modalities. The volume dependent constraints (e.g., V_{20Gy}) were not incorporated in the MTD calculations, because rescaling would not suffice for these dose-volume-histogram dependent values, but instead, re-planning would be required, which was beyond the scope of this *in silico* planning study. To test for statistical significance, a two-sided Wilcoxon signed rank test was used with a Bonferroni-corrected p-value <0.01 to adjust for multiple comparisons. Data evaluation and statistical analysis were performed using Matlab software (v. 2016b, the Math Works, Natick, MA).

Results

Due to a technical obstacle, only twenty-four out of the 25 datasets were available for analysis.

The mean CTV was 20.7 cm^3 (range 5.34–71.01 cm^3). The anatomical distribution of the 24 lung tumors is shown in Fig. 1A–C. The mean dose to the target volumes and OARs after rescaling the dose to 99% of the CTV receiving at least 60 Gy is shown in Table 1. Mid-CTV dose distributions for a typical case are shown in Fig. 2. The D_{mean} and $D_{2\%}$ to the CTV were significantly lower for DSP and IMIT than for IMRT, reflecting a better dose homogeneity with particles (p = 0.002 and p = 0.004, respectively, for DSP; p < 0.001 and p < 0.001, respectively, for IMIT; Table 1). D_{mean} and $D_{2\%}$ were higher in the Cyberknife plans compared to IMRT (both p < 0.001). The CNs revealed worse conformality for the DSP plans, for the tested 50%, 80% and 90% isodose levels (Table 1).

While prescribing the same dose to the target, most modalities had no problems adhering to the predefined objectives for OARs in most patients. In select cases, however, clear differences were noted between the modalities (Fig. 3A–F). For the esophagus and the spinal cord, given the relatively peripheral location of the tumors, none of the plans exceeded the predefined dose constraints. However, for the DSP and IMIT plans, the D_{mean} and $D_{0.03cc}$ to these organs decreased significantly by more than 50% compared to IMRT ($p \leq 0.001$ for all values). For VMAT, the $D_{0.03cc}$ to the spinal cord was on average 3 Gy higher than for IMRT (p = 0.006). For the heart, the D_{mean} was significantly lower for VMAT, DSP, and IMIT compared to IMRT, but was higher with

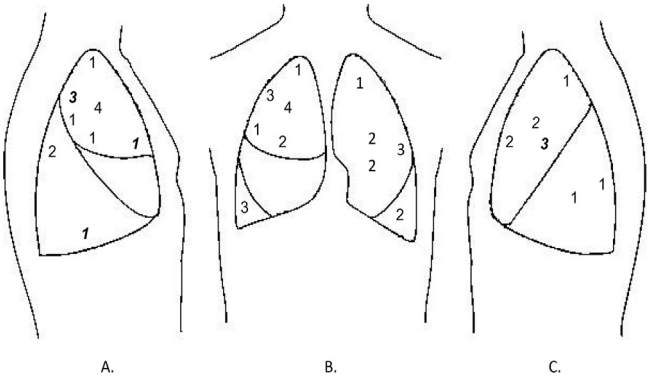

Fig. 1. (A–C) Anatomical tumor distribution of all 24 patients, (A) right lung, lateral view (14 tumors); (B) anterior view, (C) left lung, lateral view (10 tumors). In both lateral views, the bold and italic numbers represent lateral tumors. In the anterior view, the numbers in the lower lobes represent the number of tumors and not their distribution within the lower lobe (this distribution is shown in both lateral views).

CyberKnife. Heart $D_{0.03cc}$ decreased by 55% and 24% for IMIT and VMAT, respectively (p < 0.001 for both modalities). The mean lung dose (MLD) was significantly lower for VMAT and IMIT compared to IMRT (relative difference 13% and 47%, respectively, p < 0.001 for both), even though the mean absolute difference was modest. DSP occasionally resulted in a larger volume of the ipsilateral lung receiving 20 Gy or more (for example patients 9, 10, 11 and 20; Fig. 3E), resulting in a higher mean V_{20Gy} (9.7% for DSP vs 8.1% for IMRT, p = 0.008). Nevertheless, the low dose parameter for the lung, the V_{5Gy}, compared favorably with the photon modalities, for both DSP and IMIT (decrease of 39% (p < 0.001) and 59% (p < 0.001) for DSP and IMIT, respectively). The lung V_{5Gy} was also slightly, but statistically significantly, lower for VMAT when compared to IMRT (p < 0.001). Contralateral lung dose was essentially negligent for both particle therapy plans (mean V_{5Gy} of 0.018% for DSP and 0.14% for IMIT, compared with 9.9% for IMRT).

Due to predominantly peripheral tumor locations (CTV overlapped the chest wall in 13 patients), high D_{max} values were noted in the chest wall: in only 9/25 (36%) patients the $D_{0.03cc}$ was lower than the objective, for one or more of the modalities (Fig. 3F). This problem was encountered mainly in the planning of particle therapy: the $D_{0.03cc}$ to the chest wall increased significantly for both particle therapies, mainly for DSP (23% higher than IMRT, constituting an absolute 12 Gy increase in dose, p < 0.001). For all modalities, however, the mean dose to the chest wall decreased significantly compared to IMRT (19%, 21%, 15%, 55% lower for VMAT, Cyberknife, DSP and IMIT, respectively). The influence of CTV size on the dose to the lungs and mediastinal structures was assessed and compared for all modalities (refer to Supplementary Figure). The slope of the linear trendlines was comparable for most modalities, with the exception of the Cyberknife, which was consistently the steepest. Therefore, Cyberknife may not be the first choice for larger tumors.

When the D_{max} to the chest wall or ribs was considered dose limiting, dose escalation was rarely possible using the DSP technique. Out of all DSP plans, the dose could be increased for only one patient (by 4%), compared to 29%, 42%, 33% and 25% of the cases planned with IMRT, VMAT, Cyberknife and IMIT, respectively. 'Ignoring' the dose to the chest wall and ribs enabled dose escalation to an MTD for 75%, 96%, 92%, 42% and 71% of the patients for IMRT, VMAT, Cyberknife, DSP and IMIT, respectively, and dose escalation with all modalities was possible in a third of all patients (N = 8; Table 2). In the remaining patients, the $D_{0.03cc}$ to the mediastinum hampered dose escalation in 15 patients when using DSP, and the dose to a cardiac device prohibited escalation in another patient when using IMRT.

Table 1
Dose volume metrics (with SD) after rescaling to 99% of the CTV receiving 60 Gy.

	Measure	IMRT	VMAT	Cyberknife	DSP	IMIT
CTV	D_{mean} (Gy)	65.1 (1.3)	65.7 (1.7)	68.1 (1.0)*	63.6 (1.5)*	63.1 (0.44)*
	$D_{2\%}$ (Gy)	70.6 (2.8)	70.3 (2.8)	72.9 (1.5)*	67.4 (3.1)*	66.6 (1.1)*
	$D_{98\%}$ (Gy)	60.3 (0.14)	60.5 (0.31)*	60.7 (0.35)*	60.3 (0.14)	60.2 (0.052)
	$CN_{50\%}$	0.065 (0.026)	0.081 (0.026)*	0.11 (0.021)*	0.047 (0.024)*	0.11 (0.036)*
	$CN_{80\%}$	0.18 (0.06)	0.22 (0.054)*	0.22 (0.038)*	0.093 (0.041)*	0.21 (0.056)*
	$CN_{95\%}$	0.29 (0.081)	0.34 (0.07)*	0.32 (0.051)*	0.16 (0.062)*	0.28 (0.065)
Esophagus	D_{mean} (Gy)	3.1 (1.5)	2.3 (1.1)*	2.7 (1.6)	0.41 (0.94)*	0.53 (0.75)*
	$D_{0.03cc}$ (Gy)	14.5 (6.8)	11.1 (4.5)*	8.9 (5.5)*	6.2 (10.5)*	5.5 (8.2)*
Heart	D_{mean} (Gy)	1.2 (1.4)	0.91 (1.2)*	2.4 (1.8)*	0.083 (0.21)*	0.049 (0.097)*
	$D_{0.03cc}$ (Gy)	10.6 (11.5)	8.1 (8.4)*	11.8 (5.8)	12.5 (18.2)	4.8 (7.6)*
Lungs-GTV	D_{mean} (Gy)	5.3 (1.9)	4.6 (1.9)*	4.9 (2.5)	4.8 (2.0)	2.8 (1.4)*
	V_{20Gy} (%)	8.1 (3.5)	6.7 (3.4)*	5.4 (3.8)*	9.7 (3.9)*	5.3 (2.8)*
	V_{5Gy} (%)	22.8 (7.5)	19.5 (7.3)*	24.3 (12.1)	13.9 (6.0)*	9.4 (4.2)*
Ipsilateral	V_{20Gy} (%)	16.4 (7.7)	13.5 (6.9)*	10.8 (7.1)*	19.6 (8.1)*	10.5 (4.9)*
	V_{5Gy} (%)	37.2 (13.3)	35.1 (13.2)*	41.1 (18.6)	28.1 (12.0)*	18.8 (8.0)*
Contralateral	V_{5Gy} (%)	9.9 (6.1)	4.9 (5.2)*	8.3 (9.1)	0.018 (0.064)*	0.14 (0.52)*
Mediastinal structures	D_{mean} (Gy)	2.6 (1.0)	2.1 (0.77)*	3.0 (1.5)	0.77 (0.64)*	0.4 (0.24)*
	$D_{0.03cc}$ (Gy)	31.7 (11.6)	27.4 (9.9)*	27.4 (12.4)*	48.1 (18.4)*	32.9 (13.5)
Spinal_cord	$D_{0.03cc}$ (Gy)	9.7 (4.0)	13.1 (6.8)*	7.7 (5.7)*	3.7 (10.4)*	2.8 (3.2)*
Chest_wall	D_{mean} (Gy)	7.3 (3.2)	5.9 (2.8)*	5.8 (3.2)*	6.2 (3.4)*	3.3 (1.8)*
	$D_{0.03cc}$ (Gy)	52.5 (12.3)	51.0 (13.8)	52.9 (19.3)	64.5 (7.5)*	54.2 (13.3)*
	$V_{32.5Gy}$ (cm^3)	36.2 (29.7)	26.5 (26.1)*	23.6 (23.0)*	62.8 (25.9)*	17.2 (15.0)*
Ribs	D_{mean} (Gy)	11.1 (3.3)	8.9 (3.1)*	8.4 (3.7)*	10.2 (5.3)	5.4 (2.8)*
	$D_{0.03cc}$ (Gy)	51.2 (12.5)	47.3 (14.7)*	51.0 (19.9)	63.3 (7.6)*	52.8 (13.7)*

* = significant ($p < 0.01$); two-sided pairwise Wilcoxon test against IMRT, marked red if statistically significantly higher, green if lower. Abbreviations: CTV = clinical target volume, $CN_{x\%}$ = conformity number for the CTV for x% of the prescribed dose, SD = standard deviation, D_{mean} = mean dose, $D_{2\%}$ = minimum dose to 'hottest' 2% of the volume, $D_{0.03cc}$ = dose to the 'hottest' 0.03cc, V_{xGy} = percentage of the volume receiving xGy or more.

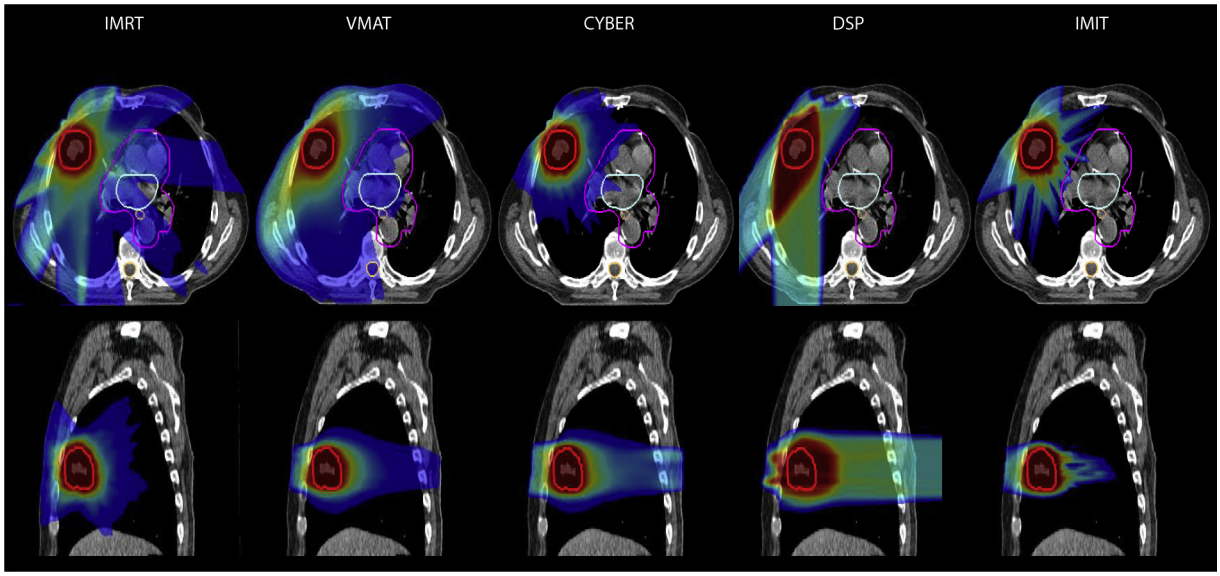

Fig. 2. Comparison of dose distribution of intensity-modulated radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), Cyberknife, Double Scattered Proton (DSP) and Intensity-Modulated Carbon-Ion (IMIT) plans.

In those 8 patients in whom dose escalation was performed, the primary dose-limiting organ was again the mediastinum (for 7 of the 8 patients, the MTD was first reached using DSP). The mean MTD to the CTV ranged widely, from 98 Gy for DSP to 205 Gy using Cyberknife. These mean MTDs for DSP and Cyberknife did not statistically significantly differ from the mean MTD of 133 Gy reached with IMRT. Similarly, the differences in mean dose to all OARs did not reach statistical significance.

Discussion

Several *in silico* planning studies are available in the literature comparing a type of stereotactic photon treatment with either carbon-ion or proton treatment for stage I NSCLC [9–11,17]. However, the current international planning study is the largest *in silico* study to date and the first to compare multiple photon-based stereotactic radiotherapy plans (IMRT, VMAT and Cyberknife) with each other and with multiple particle therapy plans (DSP, IMIT) for early stage NSCLC.

In general, most OAR doses could be reduced using particles with IMIT offering the greatest benefit. However, VMAT and Cyberknife also allowed for reduced doses to most OARs compared with IMRT. Although DSP achieved the lowest mean esophageal dose among all modalities, DSP performed worst for several important OARs, including the lung V_{20Gy} and D_{max} to the chest wall and mediastinal structures, negatively impacting on the dose escalate possibility. This is likely the result of the mostly two-beam set-up of the DSP plans, entailing higher proton beam entry doses and a loss of conformality, and these doses likely would have been

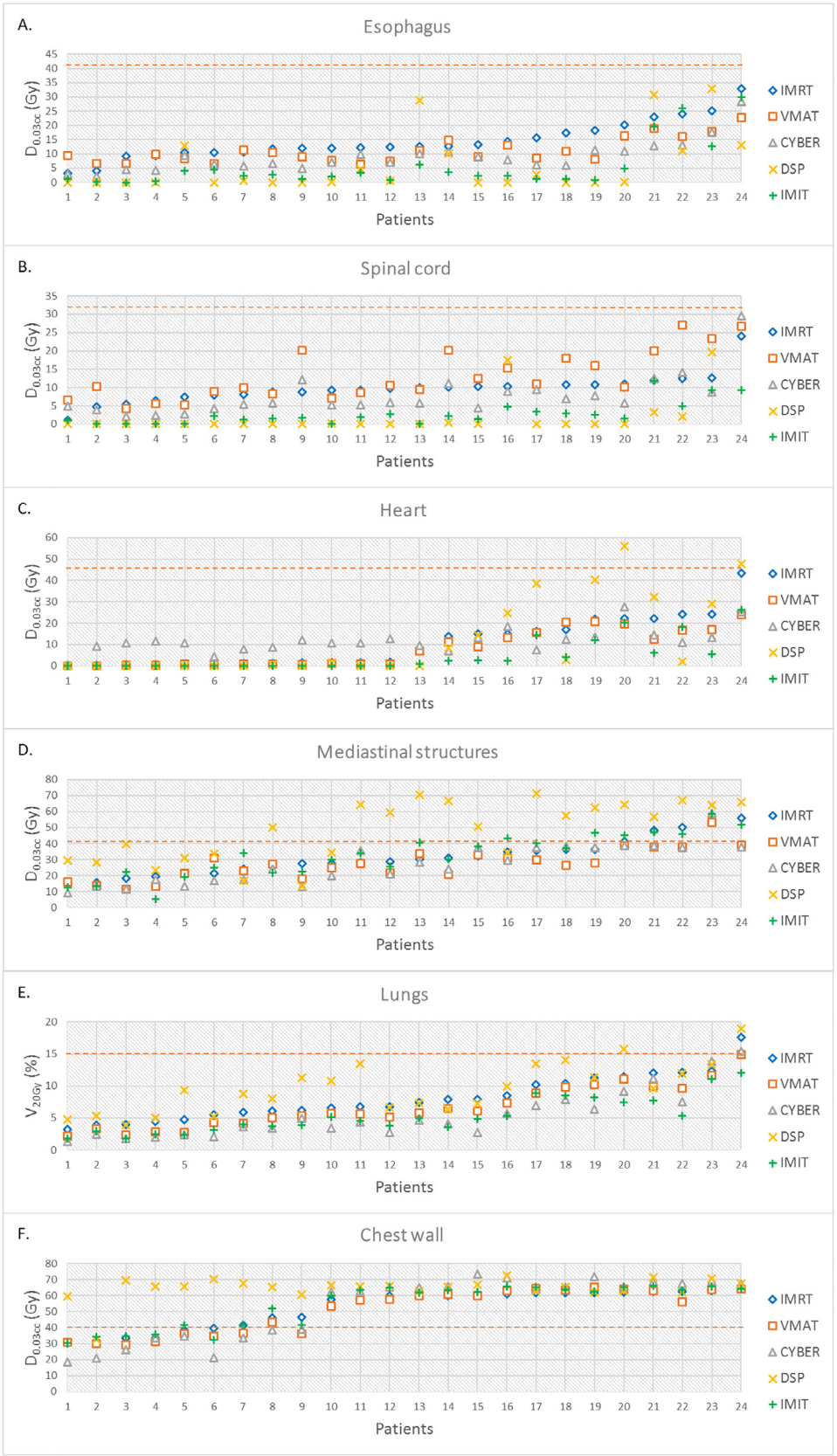

Fig. 3. (A–F) Comparison of dose to the organ at risk (OAR) per patient for each modality, sorted by lowest to highest IMRT dose. Please note that the patient numbers do not correspond between the figures. The constraint or objective used for treatment planning is displayed as a red dashed line. Abbreviations: $D_{0.03cc}$ = minimum dose to the 'hottest' 0.03 cc, V_{20Gy} = percentage receiving 20 Gy.

Table 2
Dose volume metrics (with SD) for the eight patients for whom dose escalation to a maximum tolerated dose (MTD) was possible with all modalities.

	Measure	IMRT	VMAT	Cyberknife	DSP	IMIT
CTV	D_{mean} (Gy)	133.4 (29.2)	146.1 (40.7)	204.9 (51.8)	98.0 (42.7)	180.9 (132.2)
	$D_{2\%}$ (Gy)	144.2 (30.0)	156.2 (43.1)	221.8 (60.3)	103.1 (48.2)	191.2 (138.9)
	$D_{98\%}$ (Gy)	123.9 (27.3)	134.4 (37.5)	182.2 (46.9)	93.4 (38.6)	172.3 (125.4)
	$CN_{50\%}$	0.061 (0.025)	0.075 (0.024)	0.1 (0.023)	0.044 (0.018)	0.099 (0.033)
	$CN_{80\%}$	0.17 (0.058)	0.21 (0.053)	0.2 (0.04)	0.1 (0.04)	0.19 (0.054)
	$CN_{95\%}$	0.27 (0.074)	0.32 (0.07)	0.3 (0.055)	0.17 (0.056)	0.27 (0.068)
Esophagus	D_{mean} (Gy)	4.4 (2.2)	3.9 (1.4)	5.8 (3.3)	0.44 (0.94)	1.0 (1.1)
	$D_{0.03cc}$ (Gy)	21.8 (8.6)	19.4 (2.7)	19.9 (6.7)	7.8 (13.1)	8.4 (8.6)
Heart	D_{mean} (Gy)	2.4 (2.6)	2.4 (3.0)	6.4 (3.7)	<0.01 (0.014)	0.091 (0.12)
	$D_{0.03cc}$ (Gy)	17.9 (17.3)	15.6 (15.9)	32.2 (6.1)	5.9 (8.9)	8.5 (12.3)
Lungs-GTV	D_{mean} (Gy)	9.6 (3.6)	9.2 (4.8)	12.4 (5.1)	7.4 (5.7)	8.0 (10.4)
	V_{20Gy} (%)	13.1 (5.3)	11.9 (6.2)	16.1 (7.9)	11.4 (5.7)	7.6 (5.2)
	V_{5Gy} (%)	32.5 (11.3)	34.3 (12.6)	44.1 (15.9)	16.1 (8.8)	12.5 (6.7)
Ipsilateral	V_{20Gy} (%)	24.9 (10.1)	22.7 (11.1)	29.2 (14.3)	21.6 (10.1)	14.4 (9.4)
	V_{5Gy} (%)	45.1 (14.7)	43.6 (15.3)	61.1 (21.6)	30.5 (15.6)	22.8 (11.4)
Contralateral	V_{5Gy} (%)	19.2 (8.6)	24.3 (10.2)	26.5 (14.8)	<0.01 (<0.01)	1.3 (1.8)
Mediastinal structures	D_{mean} (Gy)	4.2 (1.4)	3.9 (1.5)	7.1 (2.8)	0.36 (0.27)	0.54 (0.26)
	$D_{0.03cc}$ (Gy)	41.0 (<0.01)	38.7 (6.4)	41.0 (0.011)	41.0 (<0.01)	41.0 (0.013)
Spinal_cord	$D_{0.03cc}$ (Gy)	18.0 (8.2)	20.7 (7.0)	16.6 (5.8)	(7.5)	2.8 (2.9)

Abbreviations: CTV = clinical target volume, $CN_{x\%}$ = conformity number for the CTV for x% of the prescribed dose, D_{mean} = mean dose, $D_{2\%}$ = minimum dose to 'hottest' 2% of the volume, $D_{0.03cc}$ = dose to the 'hottest' 0.03 cc, V_{xGy} = percentage of the volume receiving xGy or more.

reduced if 3 or 4 field plans had been utilized. Furthermore, it may well be possible to further reduce these D_{max} and other OAR doses using pencil beam scanning (PBS) and intensity-modulated proton therapy, but this was beyond the scope of the comparative *in silico* study [18]. Conversely, the beam set-up and the finite range of the proton beams resulted in less low dose spillage and thus the lowest V_{5Gy} of the contralateral lung, which, together with the D_{mean} of the contralateral lung have been linked to the incidence of radiation pneumonitis in several studies [19–21]. The mean and maximum doses to the heart were also lowest using particles, which is favorable when attempting to decrease cardiovascular events and deaths in the long-term [22]. Even though the heart dose was considered less relevant for lung cancer patients, recently improved outcome rates have turned the radiation-associated heart disease into a relevant outcome with multiple recent studies demonstrating this side-effect to occur earlier than previously assumed in patients with locally advanced NSCLC [23,24]. For stage I NSCLC patients, who can potentially be long-term survivors, minimizing the dose to the heart is of even greater importance. Stam et al. [25] recently report that in particular doses to the upper region of the heart (atria and vessels) are significantly associated with non-cancer death in early stage NSCLC patients having undergone SBRT.

For this *in silico* planning study, datasets of patients who have actually been treated with photon SBRT were used for treatment planning. Therefore, most tumors were located peripherally in the lung, as no one consensus for the delivery of SBRT for centrally located tumors in close proximity to the main airways, the heart or great vessels, or the esophagus exists [26–30]. The ongoing European Organization for Research and Treatment of Cancer (EORTC) sponsored 22113-08113-LungTech study is evaluating the safety and effectiveness of photon SBRT in patients with inoperable and centrally located early stage NSCLC [31]. For small, peripherally located tumors, however, the risk of serious toxicity with SBRT is low as the tumors are usually located far away from critical tissue [32]. Hence, particle therapy is not likely to be advantageous for the unselected patient with a small, peripheral lesion. Any potential clinical benefits are likely to be small and not likely to outweigh the extra treatment costs for state-of the art particle treatment that has limited availability. As such, patients with tumors located near the thoracic wall may be best served with the modern VMAT and Cyberknife techniques, as DSP might even be disadvantageous for some patients due to the high maximum doses in the chest wall and mediastinal structures.

Correspondingly, the Particle Therapy Co-operative Group (PTCOG) concluded in its consensus statement on proton therapy in lung cancer that it rarely improves dosimetry in a clinically meaningful way in patients with small peripheral lesions. They attribute this to a lower stopping power of the protons in lung parenchyma consequently resulting in a higher exit dose [33]. The PTCOG suggests that stereotactic radiotherapy with protons or carbon ions may be more clinically beneficial in patients with a centrally located tumor (where protons have mediastinal soft tissue to stop in), a large primary tumor (>5 cm), multiple tumors or in case of re-irradiation [33,34]. These patients would otherwise be subjected to daily fractionated radiotherapy or be unable to receive radiotherapy. Further investigation into these subpopulations of patients with early stage NSCLC is warranted [35].

Our study has several limitations. First, even though tumor motion and anatomical variations are of greater influence in particle than in photon radiotherapy due to the finite range of charged particles, we did not take tumor motion into account: this was beyond the scope of our *in silico* trial. If motion amplitudes and range uncertainties were to be incorporated in the proton and carbon-ion plans, the uncertainty margins would even have been larger, especially for smaller tumors of the lower lobes [9]. This could have decreased the advantage of the particle treatments observed in this study. Conversely, a benefit might have been seen with CyberKnife planning since reduced PTV margins can be used as tumor motion is taken into account by tumor tracking.

Second, despite the ROCOCO planning protocol being adhered to, the participating centers were free to choose beam set-up and optimization criteria based on their own in-house treatment protocols. This may have led to relevant differences in the treatment planning results. To determine the influence of rescaling the dose, the analyses were repeated without rescaling, thus comparing the original plans (refer to Supplementary Table). This would not have changed the conclusions of our study.

Another limitation is the clinical applicability of IMIT for lung cancer. Even though from a dosimetric standpoint IMIT might be superior to conformal photon techniques, uncertainties regarding dose distribution and radiobiological effectiveness of carbon ions suggest a need for caution. Carbon ions are known for their high linear energy transfer and the resulting radiobiological advantage,

mainly in the Bragg peak region. However, for high doses, this effect is currently not well characterized and is the subject of ongoing research [36]. Furthermore, the availability of intensity modulated carbon ions delivered with a gantry (as used for treatment planning in the current study) is limited to the Heidelberg Ion Therapy Center in Heidelberg, the partner center of UHM.

Fourth, despite the relative differences between the doses to the OAR often being substantial, the absolute differences were relatively modest and resulting clinical significance unclear. Choosing a more expensive or less widely available modality, such as proton or carbon-ion therapy, can only be clinically worthwhile and cost-effective if the decrease in OAR dose actually results in significantly less (serious) toxicities and/or improved tumor control. For these new, costlier and less widely available techniques, the model based approach may help to carefully select patients who will likely benefit from the dose reductions achieved with particles and results feed into the rapid learning approach [35]. A step further toward personalized radiotherapy involves incorporating NTCP models in decision support systems, ensuring all dosimetric, patient, biological and other known factors influencing disease outcome and toxicities are taken into account. Prospective data registration and evaluation, *e.g.*, in the rapid learning approach, to validate and update the generated multifactorial NTCP models is essential for accurate patient selection.

In summary, the doses to the OARs for peripheral stage I NSCLC were lowest using carbon ions. Differences were often modest, however, and the clinical relevance of the reduction in dose to the OAR is unclear. In case of DSP, while mean and low dose irradiation was uniformly reduced, the maximum doses to the chest wall and ribs were significantly higher than with IMRT. VMAT and Cyberknife allowed for dose sparing of several OARs compared with IMRT. Therefore, the incremental additional benefit of particle beam therapy for stage I NSCLC may not be the most relevant indication for proton therapy or carbon therapy. However, for central, large [37] or recurrent (previously irradiated) tumors, particle therapy could be beneficial and warrants additional investigation.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.02.024.

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