Photons or protons for reirradiation in (non-)small cell lung cancer: results of the multicentric ROCOCO in silico study

Troost, E.G.C.; Wink, K.C.J.; Roelofs, E.; Simone, C.B.; Makocki, S.; Lock, S.; ... ; Ruysscher, D. de

BJR

https://doi.org/10.1259/bjr.20190879

Received: 15 October 2019 | Revised: 29 November 2019 | Accepted: 03 December 2019

Cite this article as:
Troost EG.C, Wink KC.J, Roelofs E, Simone CB, Makocki S, Löck S, et al. Photons or protons for reirradiation in (non-)small cell lung cancer: Results of the multicentric ROCOCO *in silico* study. *Br J Radiol* 2020; **93**: 20190879.

PROTON THERAPY SPECIAL FEATURE: FULL PAPER

Photons or protons for reirradiation in (non-)small cell lung cancer: Results of the multicentric ROCOCO *in silico* study

[1,2,3,4,5]ESTHER G.C. TROOST, MD, PhD, [6,7]KRISTA C.J. WINK, [6]ERIK ROELOFS, [8,9]CHARLES B. SIMONE II, MD, [1,3]SEBASTIAN MAKOCKI, [1,3,4]STEFFEN LÖCK, [10]PETER VAN KOLLENBURG, [11,12]DAVID DECHAMBRE, [13]ANDRE W.H. MINKEN, [6]JUDITH VAN DER STOEP, [8]STEPHEN AVERY, [11]NICOLAS JANSEN, [8,14]TIMOTHY SOLBERG, [10]JOHAN BUSSINK and [6]DIRK DE RUYSSCHER

[1]Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[2]Institute of Radiooncology - OncoRay Helmholtz-Zentrum Dresden - Rossendorf, Dresden, Germany
[3]OncoRay, National Center for Radiation Research in Oncology, Dresden, Germany
[4]German Cancer Consortium (DKTK), partnersite Dresden, Dresden, and German Cancer Research Center (DKFZ), Heidelberg, Germany
[5]National Center for Tumour Diseases (NCT), Partner Site Dresden, Dresden, Germany
[6]Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands
[7]Department of Radiation Oncology, Leiden University Medical Center, Leiden, The Netherlands
[8]Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA
[9]Department of Radiation Oncology, New York Proton Center, New York, USA
[10]Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands
[11]Department of Radiation Oncology, University Hospital of Liege (CHU), Liege, Belgium
[12]Radiotherapy Department, Cliniques universitaires Saint-Luc, Brussels, Belgium
[13]Radiotherapiegroup Deventer, Deventer, the Netherlands
[14]Department of Radiation Oncology, University of California, San Francisco, CA, USA

Address correspondence to: Prof. Dr. Esther G.C. Troost
E-mail: *esther.troost@uniklinikum-dresden.de*

Objective: Locally recurrent disease is of increasing concern in (non-)small cell lung cancer [(N)SCLC] patients. Local reirradiation with photons or particles may be of benefit to these patients. In this multicentre *in silico* trial performed within the Radiation Oncology Collaborative Comparison (ROCOCO) consortium, the doses to the target volumes and organs at risk (OARs) were compared when using several photon and proton techniques in patients with recurrent localised lung cancer scheduled to undergo reirradiation.

Methods: 24 consecutive patients with a second primary (N)SCLC or recurrent disease after curative-intent, standard fractionated radio(chemo)therapy were included in this study. The target volumes and OARs were centrally contoured and distributed to the participating ROCOCO sites. Remaining doses to the OARs were calculated on an individual patient's basis. Treatment planning was performed by the participating site using the clinical treatment planning system and associated beam characteristics.

Results: Treatment plans for all modalities (five photon and two proton plans per patient) were available for 22 patients (N = 154 plans). 3D-conformal photon therapy and double-scattered proton therapy delivered significantly lower doses to the target volumes. The highly conformal techniques, *i.e.*, intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), CyberKnife, TomoTherapy and intensity-modulated proton therapy (IMPT), reached the highest doses in the target volumes. Of these, IMPT was able to statistically significantly decrease the radiation doses to the OARs.

Conclusion: Highly conformal photon and proton beam techniques enable high-dose reirradiation of the target volume. They, however, significantly differ in the dose deposited in the OARs. The therapeutic options, *i.e.*, reirradiation or systemic therapy, need to be carefully weighed and discussed with the patients.

Advances in knowledge: Highly conformal photon and proton beam techniques enable high-dose reirradiation of the target volume. In light of the abilities of the various highly conformal techniques to spare specific OARs, the therapeutic options need to be carefully weighed and patients included in the decision-making process.

INTRODUCTION

Patients with lung cancer may develop a second primary lung tumour or recurrent disease after primary radiotherapy. In fact, approximately one-quarter of all patients treated for lung cancer will subsequently suffer from a second primary lung cancer and 30–50% of patients with locally advanced (non-)small cell lung cancer (NSCLC) patients treated with definitive radiation therapy and chemotherapy will have a locoregional failure.[1] In cases of isolated localised recurrences or new primary lung cancers, re-irradiation can be considered and may represent the only chance of cure in these patient populations.[2,3]

Due to the physical advantages of ions, particle therapy (proton and carbon-ion therapy) has the potential to inflict maximum damage on tumours with limited collateral damage to neighbouring healthy tissues. Previous publications on the use of particle beam therapy for lung cancer patients have shown encouraging results.[4] With more advanced techniques such as particle therapy, mitigating or compensating for intrafractional movement of the target volume and for any interfractional anatomical changes are critical for (N)SCLC patients.[5,6] In order to avoid detrimental acute and chronic toxicity, doses to critical organs such as the lungs, heart, large blood vessels, proximal bronchi, oesophagus and spinal cord have to be considered thoroughly in the setting of a reirradiation. The normal tissue dose constraints for reirradiation should be calculated on an individual patient's basis accounting for the doses previously received by organs at risk (OARs) from the initial irradiation course.[7] Patients with recurrent disease may benefit from particle therapy. Conversely, conventional photon-based radiotherapy has also improved over the recent years. With modern intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), high-dose, curative-intent reirradiation of the recurrent tumour is feasible while also resulting in relatively low doses to the surrounding OARs. Modern photon and particle therapy, therefore, allow for a decreased risk of radiation-induced complications and an increased likelihood of local control and ultimately cure.

To date, it is not clear to what extent patients with a second primary lung tumour or recurrent disease benefit from particle therapy compared to modern photon therapy. Therefore, it is necessary to define the possible advantages that may exist in particle therapy and whether they can outweigh the considerably higher (upfront) cost. Since comparison of treatment modalities cannot be achieved for an individual patient, we conducted a series of *in silico* trials for different disease entities and therapeutic settings.[8–11] In this study, we present the data of a multicentre *in silico* trial performed within the radiation oncology collaborative comparison (ROCOCO) consortium, comparing the dose to the target volume and the surrounding OARs using several photon and proton techniques in patients with recurrent localised lung cancer scheduled to undergo reirradiation.

PATIENTS AND METHODS

Patients

24 consecutive patients with a second primary (N)SCLC or recurrent disease after curative-intent, standard fractionated radio(chemo)therapy, treated at MAASTRO clinic (Department of Radiotherapy, Maastricht University Medical Centre+, The Netherlands) between 2006 and 2014, were included in this *in silico* planning study. The study was approved by the Institutional Review Board of MAASTRO clinic.

Delineation of target volumes and organs at risk

The tumour volumes and OARs were centrally (re)contoured in the mid-ventilation phase of a four-dimensional ^{18}F-fluorodeoxyglucose PET-CT (4D-FDG-PET-CT) scan (CT in soft tissue and lung window-width/window-level-setting) with patients positioned supine with their arms above the head using an arm-rest and leg support. The CT data consisted of non-overlapping 2–3 mm slices with a maximum image resolution of 512 × 512 mm. The CT encompassed the entire thorax in order to obtain accurate dose-volume histogram data of the intrathoracic OARs. The image datasets and delineated contours were made available to all participating sites guaranteeing uniformity.

The gross tumour volume (GTV) included all detectable gross disease, the clinical target volume (CTV) comprised the GTV with a 5 mm margin encompassing microscopic tumour extension, subsequently corrected for anatomical boundaries. The planning target volume (PTV) was constructed using an isotropic 10 mm margin around the CTV. For evaluation purposes, the PTV was clipped 3 mm below the outer body contour to compensate for the photon build-up effect. In this setting of re-irradiation, a wide range of OARs was contoured to enable calculation of doses to these OARs and the remaining body. We contoured the ipsilateral and contralateral lung separately as well as together, subtracting the GTV for dose evaluation. The heart, spinal cord, oesophagus, trachea, main bronchi, bilateral brachial plexus, ribs and chest wall were also contoured. A "mediastinal envelope" structure was also contoured that compromised the heart/pericardium, large vessels, trachea, main bronchi and oesophagus, and was expanded to a planning risk volume (PRV) using a margin of 5 mm to correct for setup inaccuracies (PRV mediastinal envelope).[11]

Treatment planning

For each patient, five photon plans (3D-conformal radiotherapy [3D-CRT]; IMRT; VMAT; TomoTherapy; and CyberKnife) and two proton plans (double scattered proton therapy [DSPT]; and intensity modulated proton therapy [IMPT]) were calculated at MAASTRO clinic (VMAT), University Hospital Carl Gustav Carus Dresden (3D-CRT and DSPT), Radboud University Medical Center (IMRT), the Centre Hospitalier Universitaire de Liège (CyberKnife), Radiotherapiegroup Deventer (TomoTherapy), and the Hospital of the University of Pennsylvania (IMPT), respectively.

Treatment planning was performed according to protocol, keeping within the tolerance doses of the OARs. Based on the delivered dose during the individual patient's first treatment course and the interval between the first and second course of irradiation, individual OAR dose constraints were determined for each patient (Supplementary Table 1) using the dose and dose-volume constraints reported in Table 1. The remaining

Table 1. Organ at risk dose constraints used for calculating the possible remaining dose depending on the interval between first and second course of irradiation

Organ at risk	Time between two irradiation series	Maximal summed dose (D_{max}; Gy) in 2 Gy fractions	Maximal dose (D_{max}; Gy) allowed for second radiation in 2 Gy fractions	Volume allowed more than the maximum dose in the second radiation plan
Spinal cord	0.75–5 years	65	45	0.03 cc
	>5 years	75	45	0.03 cc
Oesophagus	9 months or more	100	65	0.03 cc
Mediastinal envelope	9 months or more	110	70	0.03 cc
Trachea	9 months or more	110	70	0.03 cc
Brachial plexus[a]	9 months or more	85	60	0.03 cc
Organ at risk	Time between two irradiation series	**Mean** summed dose (D_{mean} in Gy)	**Mean** dose second irradiation (Gy)	
Lungs	9 months or more	22	18 V_{20Gy}<50%	
Contralateral lung			V_{5Gy} <60%	
Heart	9 months or more	70	46	

PRV, planning risk volume; GTV, gross tumour volume; D_{max}, maximum dose; D_{mean}, mean dose; V_{xxGy}, volume of organ at risk (in %) receiving a dose of xx Gy.

[a]Only take constraint into account for patients where the brachial plexus is contoured (this automatically means that the plexus is close to the PTV). For the other patients, the plexus should be avoided as much as possible.

equivalent dose in 2 Gy fractions (EQD2) to the PTV was calculated for every patient, being at least 54 Gy in 1.8 Gy fractions. The following priorities were set for the objectives (numbered in order of decreasing importance): 1 = spinal cord, 2 = PRV mediastinal envelope, 3 = heart, 4 = brachial plexus, 5 = lungs, 6 = ribs and chest wall.

Each centre used their own, clinically commissioned treatment planning system assuring state-of-the-art dose calculations. The dose was prescribed to the given PTV. Planning objectives were in accordance with several multi-institutional trials (*e.g.*, RTOG 0618 and RTOG 0236), where at least 99% of the PTV should receive at least 95% of the prescribed dose, and the maximum dose (D_{max}) should not exceed 140%. According to the study protocol, the dose to the CTV was also evaluated.

Photons

The VMAT plans were created using Eclipse v. 11.0 (Varian Medical Systems, Palo Alto, CA). The plans generally consisted of two 180° arcs with energies of 10 MV. The 3D-CRT treatment plans were generated using 6 MV and 15 MV photons and the treatment planning system Oncentra OTP v. 4.3 (Elekta, Stockholm, Sweden). The step-and-shoot IMRT plans were calculated using Pinnacle v. 9.6 (Philips Radiation Oncology Systems, Fitchburg, WI). Five to seven (mainly equally spaced) 10 MV photon beams were employed, avoiding beam entrance through the contralateral lung. 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). TomoTherapy treatment plans were created using the Accuray Hi-Art Planning Station (v5.1.0.4, Accuray). The 6 MV helical TomoTherapy plans were calculated using a pitch of 0.287 and a 2.5 cm slit width modulated by 64 binary multileaf collimators.

Protons

The DSPT plans were calculated using Oncentra XiO® v. 5.00.01 (Elekta) taking into account an relative biological effectiveness (RBE) of 1.1 and 2–3 beams of 100–226.7 MeV such that the contralateral lung and critical OARs were avoided as much as possible. For calculation of the IMPT plans, Eclipse v. 11.0 (Varian Medical Systems) was used. The field size was limited to 12 cm. Beam arrangements were chosen based on the path of least variation. Portals were designed to avoid OARs distal to the target. Plans with 2–3 fields were created as a trade-off between treatment time and target conformity. The energy-dependent spot size used in clinical practice was applied. For all proton plans, since the plans were calculated for the PTV as opposed to the CTV, no additional margins for robustness, range and positioning uncertainty were taken into account.

Data storage and analysis

The multicentric *in silico* trials In Radiotherapy (MISTIR) framework was used for data storage and exchange. The participating ROCOCO partners downloaded the datasets from the MISTIR database to perform treatment planning. After completion of the treatment plans, the dose matrices were reuploaded to the database in Digital Imaging and Communication in Medicine (DICOM) format. The dose-volume metrics were extracted and compared to the VMAT plans, which were considered as the "gold standard." Of the following parameters, the ones relevant for the CTV, PTV and OAR were compared among the treatment plans: mean dose

(D_{mean}); minimum dose to the "hottest" 0.03 cc ($D_{0.03cc}$, near maximum dose), highest dose to 2% of the volume ($D_{2\%}$, near maximum dose); lowest dose to 99% of the volume ($D_{99\%}$, near minimum dose); volume of a structure receiving a radiation dose of xx Gy (V_{xxGy}) given in cc.

The evaluation of the results was based on 1) the original treatment plans, in which no target dose rescaling was performed, since both the remaining dose to the OARs for the individual patients and the doses achieved in the target volumes varied, and 2) rescaling to the maximally tolerable dose achievable until the first OAR dose constraint was reached. Differences in dose-volume parameters were tested for statistical significance between VMAT and the other irradiation techniques using the paired Wilcoxon signed-rank test (R Statistics 3.3.2, R Foundation for Statistical Computing, Vienna). The *p*-values were corrected for multiple testing by the Bonferroni method, accounting for the six comparisons per dose-volume parameter. Two-sided tests were performed and *p*-values < 0.05 were considered as statistically significant.

RESULTS

In total, 24 complete patient data sets including all treatment modalities were available for statistical analysis. For one of the 24 patients, an electron instead of a photon treatment plan was calculated for the 3D-CRT technique. For another patient, two identical IMPT plans were calculated but named differently. Therefore, across all techniques, only 22 treatment plans were available for analysis of the dose to the target volumes and OARs.

For all comparisons, VMAT plans served as reference. For the original plans without rescaling, compared to VMAT, the overall $D_{0.03cc}$ in the PTV was statistically significantly lower for 3D-CRT, IMRT, TomoTherapy and DSPT, similar for IMPT and significantly higher for CyberKnife (Table 2). The $D_{99\%}$ was similarly high for VMAT, IMRT, CyberKnife, TomoTherapy and IMPT, and significantly lower for the 3D-CRT and DSPT treatment plans. For the CTV, the D_{mean}, $D_{99\%}$ and $D_{0.03cc}$ were significantly lower for the 3D-CRT and DSPT treatment plans.

Table 2. Median dose to target volumes and organs at risk delivered with the respective treatment modalities

		VMAT	3D-CRT	IMRT	CYBER	TOMO	DSPT	IMPT
CTV	$D_{0.03cc}$	59.7	57.6**	58.8*	73.4**	55.8**	56.0**	60.3
	D_{mean}	55.4	53.3**	55.1	63.2*	53.8**	53.3**	57.0*
	$D_{99\%}$	52.9	44.8**	52.8	55.8	52.7	42.3**	53.5
PTV	$D_{0.03cc}$	60.7	58.1**	59.2*	73.4**	57.1**	56.2**	60.5
	D_{mean}	55.6	52.3**	54.9*	61.8	54.0*	53.3**	56.3
	$D_{99\%}$	51.3	39.4**	51.4	51.5	51.9	39.3**	51.4
Spinal cord	$D_{0.03cc}$	23.8	20.4*	24.2	14.3	21.1	18.9**	17.5**
Oesophagus	$D_{0.03cc}$	47.8	31.6*	44.8	43.0	47.7	34.0**	51.7
	D_{mean}	10.8	7.1*	12.2	11.7*	10.7	3.2**	8.1*
Mediastinal envelope	$D_{0.03cc}$	58.5	47.2**	57.8	66.9*	54.8	46.9**	57.5
Trachea	D_{mean}	10.7	6.3*	9.5	11.2**	10.0	2.5**	4.9
	$D_{0.03cc}$	45.7	31.0*	41.0	42.4	44.0	35.5*	44.2
Left bronchus	D_{mean}	16.9	15.7*	19.2	17.1	16.3	9.1**	10.4**
	$D_{2\%}$	35.9	33.3*	36.5	43.2*	40.7	24.7**	47.7
Right bronchus	D_{mean}	16.0	13.6*	12.6	12.1*	15.0	3.5*	11.4
	$D_{2\%}$	35.4	28.7*	24.1	23.2*	21.0	17.6*	33.7
Lungs	D_{mean}	6.2	6.0	6.4*	7.6*	7.0	3.7**	3.8**
	V_{20Gy}	8.7	9.6	11.1*	8.4	10.0	7.4	7.4*
	V_{5Gy}	33.8	25.3*	33.8	44.2*	38.7	13.5**	13.5**
Heart	D_{mean}	1.6	2.3	3.0*	3.6	3.4*	0.3**	0.37**
	V_{20Gy}	0.1	0.6	2.1	0.0	2.0	0.0	0.3
	V_{5Gy}	8.0	10.5	13.5	26.7	11.8*	1.7*	1.9*
Integral body	D_{mean}	4.4	4.0	4.9**	5.3**	5.1**	2.9**	2.3**

CTV, clinical target volume;$D_{2\%}$, highest dose to 2% of the volume; $D_{99\%}$, lowest dose to 99% ofthe volume; D0.03cc, minimum dose to the 'hottest' 0.03; D_{mean}, mean dose to structure; PTV, planning target volume;V_{xxGy}, volume of a given structure receiving a radiation dose of xx Gy. Outcomes are reported in Gy (dose) or percentage (volume). * represents $p<0.05$, ** $p<0.001$, when compared to VMAT, respectively.

For the overall radiation dose values to the OARs, clinically relevant differences were also observed (Table 2). In the 3D-CRT plans, which achieved lower doses to the CTV and PTV (see above), the reported doses to the spinal cord, oesophagus, mediastinal envelope, trachea, bronchi and lungs (V_{5Gy}) were significantly lower compared to VMAT. In the IMRT plans, the D_{mean} and V_{20Gy} to the lungs and the D_{mean} to the heart were statistically significantly higher compared to the respective values for VMAT. CyberKnife, reaching the highest doses in the target volumes, deposited significantly higher doses in the oesophagus, mediastinal envelope, trachea, left bronchus ($D_{2\%}$) and lungs (D_{mean} and V_{5Gy}), whereas it achieved lower doses in the right bronchus. The TomoTherapy treatment plans largely resembled those of VMAT, although D_{mean} and V_{5Gy} to the heart were statistically significantly higher than with VMAT. For DSPT, the target doses were not reached in most cases, although multiple double-scattered proton beams were used. Consequently, and also due to the physical characteristics of protons, the doses to the OARs were in general lower compared to VMAT. This was true for all OARs evaluated, albeit to a varying extent. Using IMPT, lower doses to OARs were also achieved, although sufficient target coverage was reached. Doses to the spinal cord, oesophagus, left bronchus (D_{mean}), lungs (D_{mean} and V_{5Gy}) and heart (D_{mean} and V_{5Gy}) were statistically significantly lower compared to VMAT. Overall, the mean dose to the integral body was significantly lower for both proton beam techniques, and higher using any of the conformal rotational photon techniques, again when compared to VMAT.

In order to compensate for different treatment planning techniques, the plans were rescaled to maximally tolerable dose until the first OAR dose constraint was reached (Table 3). By doing so, the dose to both the CTV and PTV was revealed to not differ significantly from that of VMAT for any of the techniques. Nonetheless, it can be appreciated that both 3D-CRT and PSPT strictly kept to the OAR dose constraints and remained almost unchanged, whereas rescaling indeed lead to down-scaling in CyberKnife and TomoTherapy plans. For all except for PSPT, the integral body dose statistically significantly differed from that delivered by VMAT. Most radiation

Table 3. Median dose to target volumes and OARs after deploying rescaling to the maximum tolerated dose to the first dose-limiting OAR

		VMAT	3D-CRT	IMRT	CYBER	TOMO	DSPT	IMPT
CTV	$D_{0.03cc}$	46.6	55.9	44.4*	45.3	42.7*	55.2	47.2
	D_{mean}	43.3	48.8	41.4	39.7	41.6	50.5	44.0
	$D_{99\%}$	41.6	35.6	39.7	35.1*	40.5	41.4	41.9*
PTV	$D_{0.03cc}$	47.6	55.9	44.9*	45.4	43.5*	55.5	47.3
	D_{mean}	43.3	48.0	41.1	38.7	41.9	49.4	43.4*
	$D_{99\%}$	40.2	33.9*	36.7	31.5**	40.2	38.8	39.5
Spinal cord	$D_{0.03cc}$	15.2	14.0	15.3	8.8*	15.0	13.0	8.5*
Oesophagus	$D_{0.03cc}$	27.7	24.3	24.4	21.6*	22.7	14.5	25.3
	D_{mean}	5.5	4.4	6.3	6.1	4.8	3.1*	4.8
Mediastinal envelope	$D_{0.03cc}$	39.6	42.2	36.3	35.0	38.0	44.8	42.4
Trachea	D_{mean}	5.3	4.9	5.4	6.6	5.5	2.5	4.0
	$D_{0.03cc}$	19.8	19.2	23.9	16.5	18.9	13.5	16.4
Left bronchus	D_{mean}	9.2	9.6	14.0	9.8	8.5	7.9	8.7
	$D_{2\%}$	16.6	20.9	22.1	12.3	16.2	16.2	25.0
Right bronchus	D_{mean}	8.9	8.7	9.4	7.5	9.7	3.5	8.2
	$D_{2\%}$	12.6	11.1	13.3	12.2	14.1	9.5	13.4
Lungs	D_{mean}	4.1	5.1	4.5	4.0	4.1*	3.4*	3.1*
	V_{20Gy}	5.0	8.6*	6.5*	3.7*	5.6	6.2	5.7
	V_{5Gy}	20.2	25.1	26.2	25.8	25.2*	13.5*	11.6**
Heart	D_{mean}	1.9	2.3	2.2	1.9	2.4**	0.2**	0.3**
	V_{20Gy}	0	0.1*	0*	0	0.9*	0	0
	V_{5Gy}	6.9	10.5	10.9	10.6	8.6*	0.7	1.8*
Integral body	D_{mean}	2.3	2.6*	2.5*	2.4*	2.5**	2.3	1.5*

CTV, clinical target volume;$D_{2\%}$, highest dose to 2% of the volume; $D_{99\%}$, lowest dose to 99% ofthe volume; $D_{0.03cc}$, minimum dose to the 'hottest' 0;D_{mean}, mean dose to structure; PTV, planning target volume;V_{xxGy}, volume of a given structure receiving a radiation dose of xx Gy.
Outcomes arereported in Gy (dose) or percentage (volume). * represents $p<0.05$, ** $p<0.001$, when compared to VMAT, respectively.

doses to the assessed OARs were non-significantly different for the techniques used. Of note, the radiation dose to the heart and lungs was significantly reduced when using TomoTherapy, PSPT or IMPT, whereby this was most pronounced in the D_{mean} and V_{5Gy}, respectively.

DISCUSSION

In the setting of a reirradiation and in line with previous publications in the context of ROCOCO, the highly precise and conformal proton beam technique, IMPT, results in an equally good target coverage as VMAT, whilst reducing the dose to the OARs.[8,11] This is, to our knowledge, the first *in silico* planning study addressing this particular topic of reirradiation for (N)SCLC.

After having undergone high-dose radio(chemo)therapy with high doses to the OARs, therapeutic options in case of isolated local or (loco)regional disease are few. High-dose reirradiation is hazardous and may lead to irreversible, potentially life-threatening complications. The review by De Ruysscher et al[2] presented the studies or retrospective analyses performed and the potential detrimental effects. With more conformal radiation techniques, the occurrence of these side effects may be reduced, however, not eliminated.[12]

In the first multicentre Phase II clinical study on reirradiation with DSPT and IMPT, 6 of 57 patients developed a fatal complication, possibly (N = 3) or probably (N = 3) associated with high-dose reirradiation to centrally located critical structures and concurrent chemotherapy. The median interval between initial irradiation and reirradiation was 19 months (range 3.5–151 months), the median reirradiation prescription dose was 66.6 Gy (30–74 Gy), and 68% of patients received concurrent chemotherapy. In total, 42% of the patients developed Grade 3 or higher acute and/or late toxicities.[13] In-depth analysis revealed that overlap with the central airway region and doses to the heart and oesophagus were significantly associated with Grade ≥3 toxicities. Most patients were treated with DSPT (60%) and there was no comparison with patients treated with IMPT. In a published retrospective series on 27 patients with reirradiated thoracic cancers (excluding breast cancer) using IMPT, the risk of serious toxicity was notably lower.[14] With a median reirradiation dose of 66 Gy (range 42.3–84 Gy) and despite 81% of the tumours being localised centrally (defined as tumour ≤2 cm of any critical mediastinal structures), only 7% of the patients experienced Grade 3 pulmonary toxicity and no Grade 4 or 5 toxicities occurred. In a more recent prospective multicentre registry analysis of 79 patients with lung cancer who underwent proton reirradiation, toxicity overall was lower, with acute and late Grade 3 toxicities occurring in 6 and 1%, respectively, and three patients dying after re-irradiation from possible radiation-induced toxicity.[15]

Other therapeutic options are also being explored. These included targeted agents tailored to the tumour's molecular profile.[16–18] Moreover, immunotherapy is increasingly being used in the palliative setting, but also in the context of locally recurrent disease. Peters et al[19] summarised the use of programmed death 1 (PD-) blockade in advanced, *i.e.*, recurrent or metastatic, (N)SCLC patients. In particular pembrolizumab, a monoclonal antibody directed at PD-1 has demonstrated survival benefits in several studies across solid tumours, including in (N)SCLC. Taking it one step further, immunotherapy combined with palliative as well as high-dose reirradiation (in adjuvant setting) is a therapeutic option currently being explored.[20] Although these rather novel approaches are promising and may improve clinical outcomes, also they may harbour side effects: in the case of immunotherapy, patients may develop pneumonitis. Therefore, those patients having been treated with high-dose thoracic radio(chemo)therapy need to be monitored with particular caution.[21]

From this plethora of tailored therapeutic options and individual patients' tumour biology, it becomes clear that clinical randomised studies with fixed doses to the target and a set systemic treatment are not likely to be feasible. Instead, treatment needs to be aligned to the molecular profile of the tumour and to the remaining tolerance doses to OARs. With deformable image and dose registration algorithms, the dose from the first radiation course can be deformed to the re-irradiation planning CT, to guide dose planning and evaluation.[14,22] Additionally, factors such as the interval between initial treatment and time to recurrent disease, use of concurrent systemic therapy, as well as the experience of the treating department need to be taken into account.

This ROCOCO study holds some limitations. First, the participating centres performed the treatment planning according to a strict, previously consented, protocol. Despite this, experience of the treatment planner may have differed and thus results in varying outcomes. Also the different treatment planning systems used with their varying underlying dose-calculation algorithms may have differently influenced dose conformity, in particular since the lung is target volume. Second, although the study was based on 4D-PET-CT data, only the mid-ventilation data were used in this study and thus no internal target volume deployed. This approach was chosen since the different radiation techniques require different strategies to take tumour and anatomical motion into account. This is caused by their different sensitivity to changes in tissue density in the beam path and the accompanying variation in beam bath, *i.e.*, the interplay effect. Different strategies to overcome this hurdle are being explored, but these are beyond the scope of this treatment planning study.[6,23,24] Third, although it is not uniformly clinical practice in proton beam irradiation, treatment plans were calculated using a given PTV without considering additional uncertainty margins. Results for target coverage were nonetheless given for both CTV and PTV. This may, along with the absent of robustness analyses for proton and photon treatment plans, have influenced the dose to the OARs and thus some results. Fourth, in the absence of normal tissue complication models for proton beams, the ones established for photons were considered in calculating the remaining tolerance dose to the OARs.[7] Most importantly, these data need to be gathered and will indeed be collected within the model-based approach.[25]

In conclusion, highly conformal photon and proton beam techniques enable high-dose reirradiation of the target volume. They, however, significantly differ in the dose deposited in the OARs. The therapeutic options, *i.e.*, reirradiation or systemic therapy, need to be carefully weighed and discussed with patients.

REFERENCES

1. van Baardwijk A, Wanders S, Boersma L, Borger J, Ollers M, Dingemans A-MC, et al. Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 1380–6. doi: https://doi.org/10.1200/JCO.2009.24.7221
2. De Ruysscher D, Faivre-Finn C, Le Pechoux C, Peeters S, Belderbos J. High-Dose re-irradiation following radical radiotherapy for non-small-cell lung cancer. *Lancet Oncol* 2014; **15**: e620–4. doi: https://doi.org/10.1016/S1470-2045(14)70345-6
3. Vyfhuis MAL, Rice S, Remick J, Mossahebi S, Badiyan S, Mohindra P, et al. Reirradiation for locoregionally recurrent non-small cell lung cancer. *J Thorac Dis* 2018; **10**(Suppl 21): S2522–36. doi: https://doi.org/10.21037/jtd.2017.12.50
4. Chang JY, Verma V, Li M, Zhang W, Komaki R, Lu C, et al. Proton beam radiotherapy and concurrent chemotherapy for unresectable stage III non-small cell lung cancer: final results of a phase 2 study. *JAMA Oncol* 2017; **3**: e172032. doi: https://doi.org/10.1001/jamaoncol.2017.2032
5. Wink KCJ, Roelofs E, Solberg T, Lin L, Simone CB, Jakobi A, et al. Particle therapy for non-small cell lung tumors: where do we stand? A systematic review of the literature. *Front Oncol* 2014; **4**: 292. doi: https://doi.org/10.3389/fonc.2014.00292
6. Jakobi A, Perrin R, Knopf A, Richter C. Feasibility of proton pencil beam scanning treatment of free-breathing lung cancer patients. *Acta Oncol* 2018; **57**: 203–10. doi: https://doi.org/10.1080/0284186X.2017.1355107
7. Marks LB, Bentzen SM, Deasy JO, Kong F-MS, Bradley JD, Vogelius IS, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S70–6. doi: https://doi.org/10.1016/j.ijrobp.2009.06.091
8. Roelofs E, Engelsman M, Rasch C, Persoon L, Qamhiyeh S, de Ruysscher D, et al. Results of a multicentric in silico clinical trial (ROCOCO): comparing radiotherapy with photons and protons for non-small cell lung cancer. *J Thorac Oncol* 2012; **7**: 165–76. doi: https://doi.org/10.1097/JTO.0b013e31823529fc
9. Eekers DBP, Roelofs E, Cubillos-Mesías M, Niël C, Smeenk RJ, Hoeben A, et al. Intensity-Modulated proton therapy decreases dose to organs at risk in low-grade glioma patients: results of a multicentric in silico ROCOCO trial. *Acta Oncol* 2019; **58**: 57–65. doi: https://doi.org/10.1080/0284186X.2018.1529424
10. Eekers DBP, Roelofs E, Jelen U, Kirk M, Granzier M, Ammazzalorso F, et al. Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric in silico ROCOCO trial. *Radiother Oncol* 2016; **121**: 387–94. doi: https://doi.org/10.1016/j.radonc.2016.08.020
11. Wink KCJ, Roelofs E, Simone CB, Dechambre D, Santiago A, van der Stoep J, et al. Photons, protons or carbon ions for stage I non-small cell lung cancer - Results of the multicentric ROCOCO in silico study. *Radiother Oncol* 2018; **128**: 139–46. doi: https://doi.org/10.1016/j.radonc.2018.02.024
12. Verma V, Rwigema J-CM, Malyapa RS, Regine WF, Simone CB. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. *Radiother Oncol* 2017; **125**: 21–30. doi: https://doi.org/10.1016/j.radonc.2017.08.005
13. Chao H-H, Berman AT, Simone CB, Ciunci C, Gabriel P, Lin H, et al. Multi-Institutional prospective study of reirradiation with proton beam radiotherapy for locoregionally recurrent non-small cell lung cancer. *J Thorac Oncol* 2017; **12**: 281–92. doi: https://doi.org/10.1016/j.jtho.2016.10.018
14. Ho JC, Nguyen Q-N, Li H, Allen PK, Zhang X, Liao Z, et al. Reirradiation of thoracic cancers with intensity modulated proton therapy. *Pract Radiat Oncol* 2018; **8**: 58–65. doi: https://doi.org/10.1016/j.prro.2017.07.002
15. Badiyan SN, Rutenberg MS, Hoppe BS, Mohindra P, Larson G, Hartsell WF, et al. Clinical outcomes of patients with recurrent lung cancer Reirradiated with proton therapy on the proton Collaborative group and University of Florida proton therapy Institute prospective registry studies. *Pract Radiat Oncol* 2019; **9**: 280–8. doi: https://doi.org/10.1016/j.prro.2019.02.008
16. Sabari JK, Santini F, Bergagnini I, Lai WV, Arbour KC, Drilon A. Changing the therapeutic landscape in non-small cell lung cancers: the evolution of comprehensive molecular profiling improves access to therapy. *Curr Oncol Rep* 2017; **19**: 24. doi: https://doi.org/10.1007/s11912-017-0587-4
17. Rooney C, Sethi T. Advances in molecular biology of lung disease: aiming for precision therapy in non-small cell lung cancer. *Chest* 2015; **148**: 1063–72. doi: https://doi.org/10.1378/chest.14-2663
18. Rooney MS, Shukla SA, Wu CJ, Getz G, Hacohen N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell* 2015; **160**(1-2): 48–61. doi: https://doi.org/10.1016/j.cell.2014.12.033
19. Peters S, Kerr KM, Stahel R. Pd-1 blockade in advanced NSCLC: a focus on pembrolizumab. *Cancer Treat Rev* 2018; **62**: 39–49. doi: https://doi.org/10.1016/j.ctrv.2017.10.002
20. Evans T, Ciunci C, Hertan L, Gomez D. Special topics in immunotherapy and radiation therapy: reirradiation and palliation. *Transl Lung Cancer Res* 2017; **6**: 119–30. doi: https://doi.org/10.21037/tlcr.2017.04.03
21. Manapov F, Roengvoraphoj O, Dantes M, Marschner S, Li M, Eze C. Pneumonitis in irradiated lungs after nivolumab: a brief communication and review of the literature. *J Immunother* 2018; **41**: 96–9. doi: https://doi.org/10.1097/CJI.0000000000000198
22. Boman E, Kapanen M, Pickup L, Lahtela S-L. Importance of deformable image registration and biological dose summation in planning of radiotherapy retreatments. *Med Dosim* 2017; **42**: 296–303. doi: https://doi.org/10.1016/j.meddos.2017.06.006
23. Boda-Heggemann J, Knopf A-C, Simeonova-Chergou A, Wertz H, Stieler F, Jahnke A, et al. Deep inspiration breath Hold—Based radiation therapy: a clinical review. *Int J Radiat Oncol Biol Phys* 2016; **94**: 478–92. doi: https://doi.org/10.1016/j.ijrobp.2015.11.049
24. Bernatowicz K, Lomax AJ, Knopf A. Comparative study of layered and volumetric rescanning for different scanning speeds of proton beam in liver patients. *Phys Med Biol* 2013; **58**: 7905–20. doi: https://doi.org/10.1088/0031-9155/58/22/7905
25. Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. *Radiother Oncol* 2013; **107**: 267–73. doi: https://doi.org/10.1016/j.radonc.2013.05.007