Radiotherapy and Oncology 174 (2022) 23–29

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Ultra-fast pencil beam scanning proton therapy for locally advanced non-small-cell lung cancers: Field delivery within a single breath-hold

Vivek Maradia [a,b,*], Steven van de Water [a,c], David Meer [a], Damien C. Weber [a,d,e], Antony J. Lomax [a,b], Serena Psoroulas [a]

[a] Paul Scherrer Institute; [b] ETH Zurich, Switzerland; [c] Department of Radiation Oncology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands; [d] University Hospital Zurich; and [e] University Hospital Bern, University of Bern, Switzerland

ARTICLE INFO

Article history:
Received 14 February 2022
Received in revised form 3 June 2022
Accepted 22 June 2022
Available online 3 July 2022

Keywords:
Pencil beam scanning
Breath-hold
Treatment delivery efficiency
Proton therapy
Hypofractionation

ABSTRACT

Purpose: The use of motion mitigation techniques such as breath-hold can reduce the dosimetric uncertainty of lung cancer proton therapy. We studied the feasibility of pencil beam scanning (PBS) proton therapy field delivery within a single breath-hold at PSI's Gantry 2.

Methods: In PBS proton therapy, the delivery time for a field is determined by the beam-on time and the dead time between proton spots (the time required to change the energy and/or lateral position). We studied ways to reduce beam-on and lateral scanning time, without sacrificing dosimetric plan quality, aiming at a single field delivery time of 15 seconds at maximum. We tested this approach on 10 lung cases with varying target volumes. To reduce the beam-on time, we increased the beam current at the isocenter by developing new beam optics for PSI's PROSCAN beamline and Gantry 2. To reduce the dead time between the spots, we used spot-reduced plan optimization.

Results: We found that it is possible to achieve conventional fractionated (2 Gy(RBE)/fraction) and hypofractionated (6 Gy(RBE)/fraction) field delivery times within a single breath-hold (<15 sec) for a variety non-small-cell lung cancer cases.

Conclusion: In summary, the combination of spot reduction and improved beam line transmission is a promising approach for the treatment of mobile tumours within clinically achievable breath-hold durations.

Particle therapy has emerged as a viable treatment option for many tumors in radiotherapy. In particular, proton therapy has the potential to escalate the dose to the tumor in the treatment of lung cancers while decreasing the dose to the organs at risk (lung and heart) when compared to photon therapy [1]. Treating mobile tumors in the thorax however is currently a challenge, particularly for pencil beam scanning (PBS) [2,3], where interplay effects can cause hot and cold spots within the target and dose blurring into the surrounding normal tissues. To address these issues, various motion mitigation techniques have been proposed and employed such as breath-hold [4,5], rescanning [6,7], and gating[8]. For all these however, it is preferable to have short treatment delivery times in order for them to be most effective and efficient. This is particularly true for breath-hold, whereby typical breath-hold durations for lung cancer patients are in the order of 10–16 s [4].

In comparison to photon therapy, the potential of proton therapy with breath-hold has undergone limited exploration. A few studies however concluded that proton therapy treatment in a single breath-hold would be a safe and effective mode of treatment for moving targets [5,9,10]. Thus, more investigations into methods of reducing field delivery times for PBS proton therapy to within a single breath-hold are required.

Field delivery time in PBS proton therapy depends both on the beam-on time and the time required to change energy layers and/or lateral position (dead-time). Predominantly, beam-on time is determined by the beam intensities that can be transported through the gantry, and for cyclotron based facilities, these are typically energy-dependent at the isocenter [11,12]. At our institute for instance, for the lowest therapeutic energies (70 MeV), transmission from the cyclotron to isocenter (patient location) is only of the order of 0.1%. As such, these low transmissions for lower energies cause an undesirable increase in beam-on and field delivery time, complicating the treatment of mobile tumors. One way to reduce the field delivery time for PBS proton therapy therefore is to increase the transmission of the beam from the cyclotron to the isocenter, thereby also increasing beam intensity [10,11]. In addi-

* Corresponding author at: Center for Proton Therapy, Paul Scherrer Institute, Forschungsstrasse 111, 5232 Villigen PSI, Switzerland.
E-mail address: vivek.maradia@psi.ch (V. Maradia).

https://doi.org/10.1016/j.radonc.2022.06.018
0167-8140/

tion however, field delivery times can also be further reduced by reducing the number of proton spots delivered per field, thus additionally reducing the dead time during field delivery [13].

In this article, we experimentally investigate the potential of reducing both beam-on and dead times for the treatment of non-small-cell lung cancers, with the aim of reaching field delivery times within typical breath-hold durations for lung cancer patients. First, to reduce dead time, we employ a spot reduction optimization technique during the treatment planning process to substantially reduce the number of delivered pencil beams per field [13]. Then, to reduce the beam-on time, we have developed and implemented new beam optics for our treatment beamline and gantry to achieve factor 5 higher intensities for all energy beams [14]. To see the effect on field delivery time, we delivered plans for 10 locally advanced non-small-cell lung cancer (NSCLC) cases with both spot-reduction and high transmission beams, and compared field delivery time to those of our current clinical protocols. This was done for both conventional (2 Gy(RBE/fraction) and hypo-fractionated (6 Gy(RBE)/fraction) [15–18] regimes.

Materials and methods

Patient data

For this study, we are using the patient data which has previously been described [10,19,20], it is only briefly summarized here. The patient cohort included 10 patients (Table 1) all treated for locally advanced NSCLC with photon radiation therapy to 66 Gy (RBE) in 33 fractions over 6–7 weeks.

Treatment planning

(1). Conventional treatment planning

Clinical, 3 field single field uniform dose (SFUD) treatment plans for the PSI Gantry 2 were generated for each case, each planned on a breath-hold planning CT (with 2 mm slice spacing) scan. For all plans, our in-house treatment planning system 'PSIplan' was used with standard clinical settings [21,22].

Planning aim was to achieve a homogenous dose of 66 Gy(RBE) in 33 fractions to the target (PTV volume) whilst sparing organs at risk (OAR) as follows (the volume that received $\times$ Gy):

- Both lungs (minus the GTV): mean dose $\leq$ 20 Gy(RBE)
- Heart: mean dose $\leq$ 45 Gy(RBE)

For all plans, the spots of each field were distributed over the PTV using a rectangular grid with 4 mm lateral spacing and 2.5 mm spacing between energy layers. We used the beam size range from 2.25 mm (230 MeV) to 5 mm (70 MeV) in air at isocenter [23]. The defined dose constraints were met for all cases.

(2). Spot-reduced treatment planning

The spot-reduced treatment plans were generated according to the approach described previously by Van de Water et al. [13]. As spot reduction is not yet supported in 'PSIplan', Treatment planning was performed using the open-source toolkit 'matRad' [24], where spot reduction has been developed. The system uses the so-called 'pencil beam resampling' technique, which involves an iterative planning approach with each iteration consisting of: (1) addition of a relatively small random sample of candidate spots, (2) prioritized multi-field dose optimization [25], and (3) iterative exclusion of low-weighted spots (i.e. spots below the minimum spot weight of 10^6 protons per fraction and/or responsible for the 0.5th percentile of spot weights) until the dosimetric quality of the plan deteriorates. For all cases in this study, we used a sample size of 5000 randomly selected spots per resampling iteration, and the iterative planning process was terminated whenever all objectives were met, or none of the objectives improved by more than 3% in successive iterations.

The aim of the spot-reduced plans was to mimic, as well as possible, the conventional plans. As such, identical beam arrangements and spot grid settings (from which the spots were randomly selected) were used. Moreover, mean and maximum OAR dose values, as obtained from the conventional plan were set as objectives for the spot-reduced optimization process. Finally, additional field-specific mean-dose and variance objectives were applied for the PTV during multi-field optimization, in order to achieve similar SFUD dose contributions of the individual fields. Therefore, all the plans generated with spot-reduced planning were equivalent to SFUD plans. To enable delivery on Gantry 2, the resulting spot-reduced treatment plans were imported into 'PSIplan' from where machine control files for our gantry could be generated.

The spot reduction planning environment was used for dosimetric analysis of all plans. As an example of the dosimetric equivalence of the two planning approaches, Fig. 1 shows example dose distributions (left hand side clinical, right hand side spot-reduced) for lung case number 10. In addition, Table 2 lists PTV dose parameters for both plans of each patient. As can be seen, PTV dose coverage in the spot-reduced plans was generally similar or better than that of the clinical plans. Additionally, the homogeneity index (HI) of spot-reduced plan is better compared with PSIplan. Mean OAR doses are shown in Table 2 for lung, heart and medulla. Lung, heart and medulla dose parameters were very similar for both plans. Dose parameters for both plans (PSI plan and spot-reduced plan) were calculated with matRad.

Additionally, we performed standard robustness analysis for both (PSIplan and spot-reduced plan). Robustness against errors in patient setup and proton range was calculated by performing dose recalculations while applying isocenter shifts of 5 mm in positive and negative directions along the three principal axes, or ±5%

Table 1
Patient characteristics and comparison of number of energy layers and number of spots for two different treatment-planning optimizers (PSIplan and Spot reduced plan).

		Tumor volume				PSI plan		Spot Reduced Plan	
Patient number	NSCLC stage	GTV (cm^3)	CTV (cm^3)	PTV (cm^3)	Target location	Number of energy layers/plan	Number of spots/plan	Number of energy layers/plan	Number of spots/plan
1	T4N0M1B	35	74	137	Left Lobe	107	8405	105	798
2	T1BN2M0	46	84	154	Right Lobe	104	10,945	103	824
3	T4N3	50	94	186	Right Lobe	142	14,060	139	1163
4	TXN3M0	37	114	205	Right Lobe	126	16,394	124	1559
5	T3N0M0	88	162	267	Right Lobe	111	17,909	109	1107
6	T2BN2M0	63	158	276	Right Lobe	117	13,522	116	820
7	T4N2	54	161	307	Left Lobe	201	15,279	195	1041
8	T4N2M0	78	165	310	Right Lobe	150	19,926	147	965
9	T2BN3M0	107	202	368	Left Lobe	244	21,756	240	1743
10	T4N2M0	105	220	379	Left Lobe	151	23,427	147	1786

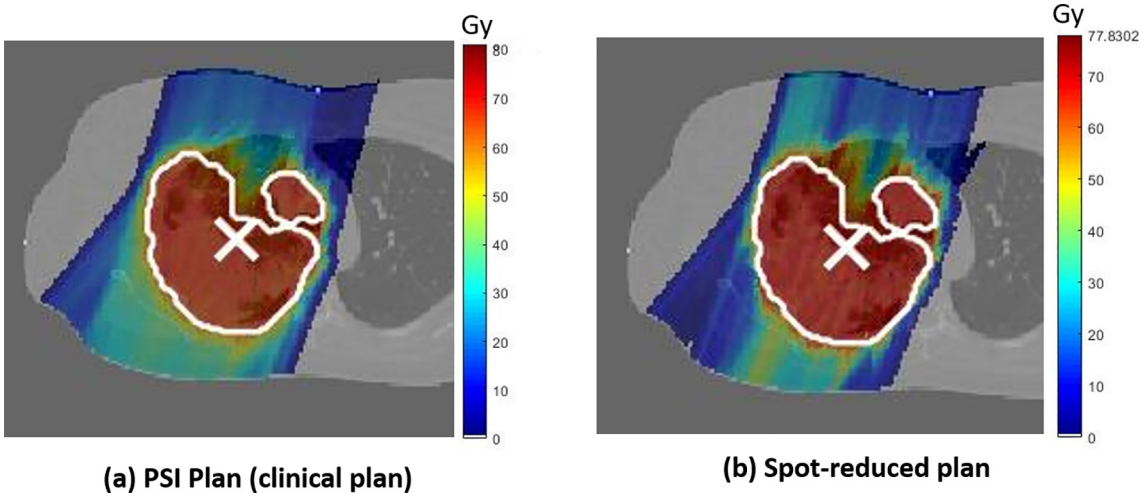


Fig. 1. Total dose distribution of lung case number 10 (PTV: 379 cm^3) with (a) PSI plan (clinical plan) and (b) spot-reduced plan.

Table 2
Comparison of dose parameters at PTV target volume and dose parameters at OAR for two different treatment-planning systems (PSIplan and SR plan (spot reduced plan)). To compare PSIplan and SR plan, *p*-value is computed based on a non-parametric Wilcoxon test for two paired samples. *P*-values below 0.05 are considered to show significant differences between PSIplan and SR plan.

	Planning target volume (PTV) dose parameters								Dose in OAR (Mean dose (%))					
	Mean dose (%)		$V_{95\%}$ (%)		$D_{2\%}$ (%)		HI (D_5/D_{95})		Dose in lung		Dose in heart		Dose in medulla	
Lung case #	PSI plan	SR plan	PSI plan	SR plan	PSI plan	SR plan	PSI plan	SR plan	PSI plan	SR plan	PSI plan	SR plan	PSI plan	SR plan
1	100.7	100.9	95.0	97.0	107.4	106.6	1.113	1.096	13	10.2	0.4	0.2	0.1	0.2
2	101.0	101.1	95.8	97.1	108.6	107.0	1.118	1.095	8.3	7.1	0.0	0.0	0.0	0.0
3	101.2	101.4	94.4	99.0	107.0	106.2	1.117	1.086	22.3	20.4	1.6	1.2	6.1	1.6
4	100.9	101.1	97.4	98.6	106.5	106.3	1.096	1.09	19.1	17.2	4.1	3.1	0.0	0.0
5	100.8	101.2	96.3	99.1	107.2	106.0	1.106	1.086	15	13.7	0.0	0.0	0.0	0.0
6	102.3	102.2	93.7	98.7	110.7	106.4	1.157	1.086	24.3	26	6.3	7.6	0.3	0.1
7	102.8	102.7	95.2	99.5	110.6	106.1	1.144	1.075	22.9	20.1	4.7	5.0	0.6	1.3
8	100.6	101.2	96.3	99.3	106.9	106.0	1.103	1.08	23.1	20.8	0.0	0.0	0.6	0.8
9	101.6	101.4	93.6	98.4	109.0	106.5	1.126	1.11	26.7	23.8	16.1	8.2	0.0	0.0
10	100.6	100.9	96.1	97.8	107.0	106.5	1.14	1.088	29.7	26.1	3.7	3.5	0.2	0.0
Mean	101.3	101.4	95.4	98.4	108.09	106.36	1.122	1.0892	20.4	18.5	3.69	2.88	0.79	0.4
SD (±)	0.76	0.59	1.23	0.88	1.56	0.31	0.02	0.01	6.59	6.47	4.92	3.17	1.88	0.61
p-value	0.0488		0.0020		0.0020		0.0020		0.0098		0.4688		1	

scaling of the relative stopping-power, respectively, resulting in eight additional recalculated error scenarios per plan. Deliberately large uncertainty parameters were used to better highlight any potential differences in robustness between the two techniques. We evaluated CTV dose-volume histograms for these dose recalculations. (Included in supplementary material).

Improving beam transmission

To complement spot-reduction, beam-on time can also be reduced by increasing the beam current at the isocenter through the development of improved beam optics for our beam line and gantry. The current clinical beam optics were designed to provide point-to-point imaging from the degrader exit to the coupling point of Gantry 2, which lead to various beam losses along the beam line. Most of the conventional beam optics of cyclotron-based proton gantries have been designed with an imaging factor between 1 and 2 from the coupling point (CP) at the gantry entrance to the isocenter, meaning that to achieve a clinically desirable (small) beam size at isocenter, a small beam size is also required at the CP. Such imaging factors are limiting the emittance/intensity which can be transported through the gantry. In our recently published articles [12,14], we propose the use of large beam size and low divergence beam at the CP along with an imaging factor of 0.5 (2:1) in a new design of gantry beam optics to achieve substantial improvements in transmission and thus increase beam intensity at the isocenter. The resulting beam currents at the isocenter were then measured as a function of energy and compared to those of the clinical optics (Fig. 2). Through this optimization process, a factor 5 higher transmission efficiency could be achieved for all proton energies (Fig. 2) whilst preserving the same beam sizes in air as for the clinically used optics. To ensure the safety of the patients, for both optics, beam intensity was kept almost constant as a function of energy by introducing intentional losses in the collimator for energies above 100 MeV (intensity compensation).

Field delivery time

All plans were delivered on the PSI Gantry 2 using both beam optics. However, the current radiation protection permit allows maximum beam current into the treatment area of 1 nA, which is the maximum current used in clinical treatment. Therefore, to measure the field delivery times for all plans delivered with the higher transmission beam optics, and to keep within this limit, all plans were scaled to deliver 5 times less dose and delivered with 5 times less beam intensity than shown by the high intensity curve in Fig. 2. As beam-on time and dose scale linearly, by this

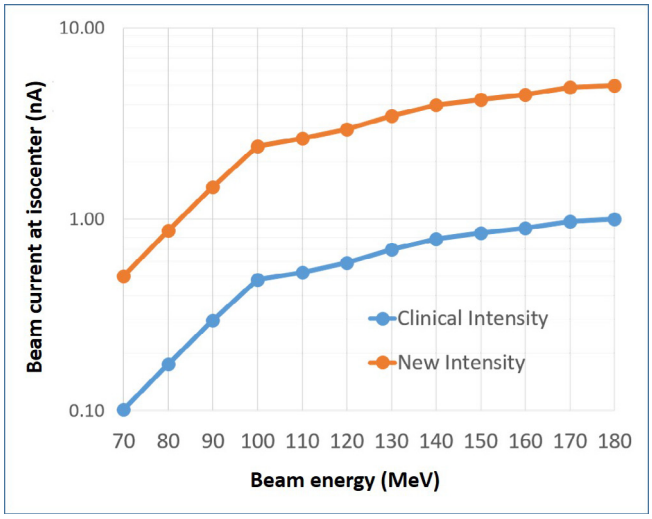


Fig. 2. Comparison of beam current at isocenter for different energy beams. Beam current is normalized for clinical beam intensity.

approach we could both experimentally validate the high transmission beam optics whilst also effectively measuring the field delivery time that would be expected in this mode without violating the 1 nA limit. For the clinical beam optics however, all plans were delivered without any modification in beam current or dose.

For each patient, we delivered all treatments in three different combinations (Table 3). Scenario A and B were delivered with the clinical beam optics while scenario C was delivered with the high transmission optics. For all scenarios, we extracted the total, beam-on and dead times from machine log-files. During all deliveries, no additional modulation of beam intensity was performed other than those imposed by the energy dependencies shown in Fig. 2. That is, there was no variation of beam intensity as a function of spot weight or minimum spot weight in an energy layer. In scenario C, the minimum spot length was about 6 ms, which is higher than the limit of minimum spot delivery length of PSI's Gantry 2 of 3 ms.

Finally, doses for all plans were scaled from 2 Gy(RBE) to 6 Gy (RBE) per fraction to simulate hypo-fractionated treatments. These were delivered once more for all scenarios and the resulting field delivery time recorded.

Results

Here we will discuss the results of the field delivery time measurements for the three different delivery scenarios. We will start with the delivery times of the *conventional fractionation* (2 Gy (RBE)/fraction) scheme and then of the *hypofractionation* (6 Gy (RBE)/fraction) scheme. For all SFUD plans studied here, the delivery times for all fields of any plan were within ±1 second of each other. Therefore, for simplicity, we report the field delivery time of only one field (field-1) for each patient case.

To investigate the feasibility of conventional fractionation proton therapy within a single breath-hold, we also delivered all scenarios with 2 Gy(RBE)/fraction. For scenario A, and as can be seen from Fig. 3(a), the total delivery time per field for all cases (independent of tumor size and shape) is equally dominated by the beam-on and spot change dead times, with the contribution from energy layer switching being less than 20% of the total delivery time. As would be expected, the delivery time per field increases as a function of tumor volume. For scenario B however, where the same transmissions have been used as scenario A but for the spot-reduced plans, beam-on time alone becomes the main contributor to delivery time and on average, we gain around 40% in delivery time compared to scenario A. Finally, for scenario C (high beam transmission and spot reduction combined) beam-on time could additionally be reduced by almost a factor of 5 compared to scenarios A and B, with energy layer switching becoming the most dominant factor. For all cases with this dose (2 Gy(RBE)/fraction), the total time to deliver each field reduces to below 10 s, even for the largest tumor. As such, we reduce delivery time by about 74% (±3.3% 1SD) averaged over all cases, when comparing scenario C to scenario A (the current clinical scenario).

To investigate the feasibility of hypofractionated proton therapy within a single breath-hold, we also delivered all scenarios rescaled to 6 Gy(RBE)/fraction, but again with the high transmission scenarios reduced by a factor 5 in dose to remain within the 1nA maximum beam current (see above). As would be expected, increasing the dose per field by a factor of 3 results in 3 times higher beam-on time compared to the conventional fractionation scheme for all scenarios (Fig. 3(b)). However, as the beam-on time now contributes more than 60% of the total delivery time per field, spot-reduction is a little less effective when combined with the clinical beam transmission (scenario B), resulting in only a 20% gain in delivery time compared to scenario A. Nevertheless, the combination of both approaches (scenario C) still reduces delivery times by ~77% (±1.9%) (averaged over all cases) compared to the clinical set-up (scenario A) and, even with these 3 times higher fraction doses, can reduce the delivery time per field to about 15 s, which is still of the order of the expected breath-hold duration for lung cancer patients [4].

Table 3
Three different combination of the treatment delivery scenario.

Delivery scenario	Treatment planning system	Beam Intensity
A	PSIplan	Clinical Intensity
B	Spot reduced plan	Clinical Intensity
C	Spot reduced plan	High Intensity

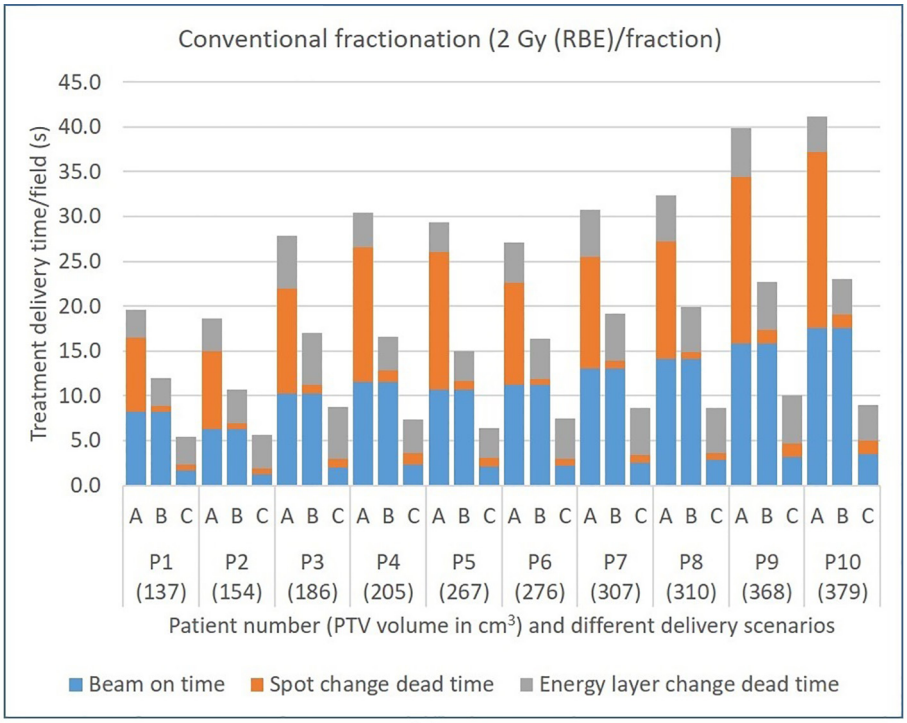
Discussion

We have demonstrated that it would be possible to deliver single fields to lung cancer cases in delivery times compatible to the expected breath-hold durations of lung cancer patients, if a combination of improved beam transmission and spot-reduction is used.

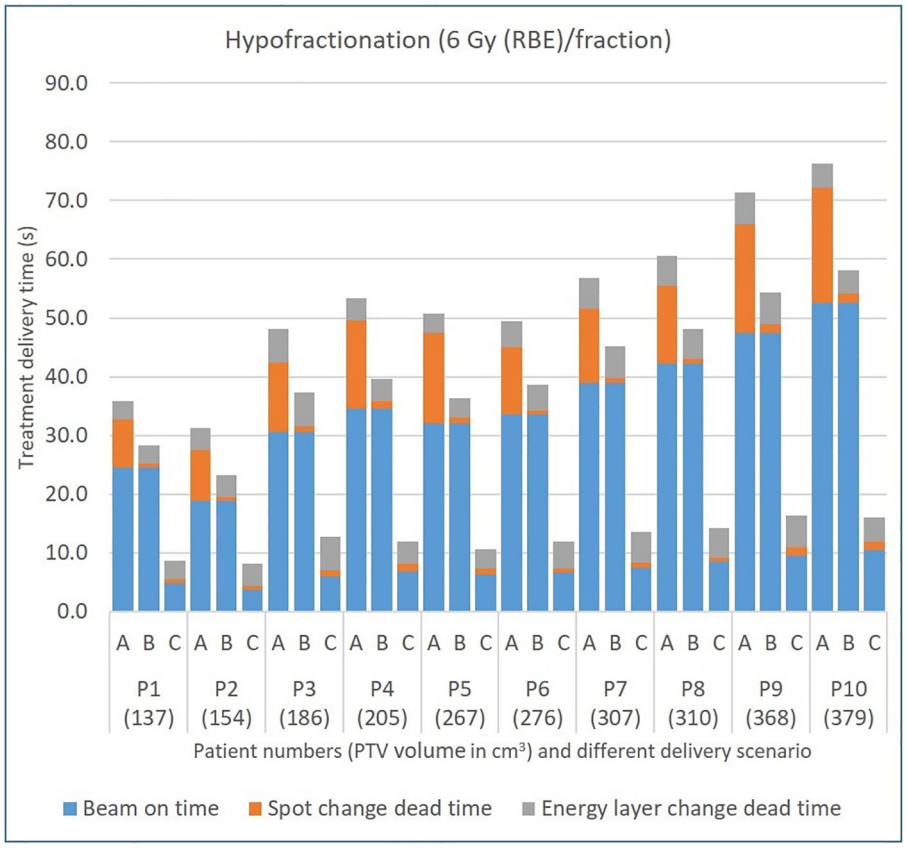
For this study, we used a large cohort of lung cancer patients (PTV volume ranging 137-379 cm^3), that allowed for an extensive experimental investigation of delivery times with both conventional fractionation (2 Gy(RBE)/fraction) and hypofractionation (6 Gy(RBE)/fraction) and have shown that, for both fractionation schemes, field delivery times could be reduced to 5–15 s depending on the tumor volume being treated.

To reduce the beam-on time, we increased the beam current reaching the patient by developing new beam optics for PSI's PROSCAN beamline and Gantry 2. Experimentally we obtained up to factor 5 higher beam current transmission while having the same beam parameters at the isocenter compared to clinically used beam intensities. In scenario C, spot-reduced plans were then delivered using these improved optics, resulting in beam-on time reductions of a factor 5, and overall reduction in delivery time by 75% and 50% compared to scenario A and scenario B respectively.

In the feasibility study for hypofractionated (6 Gy(RBE)/fraction) treatment delivery, we also showed that, based on the size and shape of the tumor, the use of high-intensity beams with spot reduction reduces the field delivery time by on average 75% compared to the clinical scenario, allowing to deliver the fields in a single breath-hold (5–15 seconds).



(a)



(b)

Fig. 3. Field delivery time for (a) conventional fractionation and (b) hypofractionation per field for different treatment planning methods and beamline optimizations. P# represents the patient number. A, B and C represents the three delivery scenarios. A = PSIplan + clinical intensity, B = spot reduced plan + clinical intensity and C = spot reduced plan + high intensity.

By improving the beam optics design of the PROSCAN beamline and Gantry 2 we managed to get factor 5 high beam transmission from the cyclotron to the isocenter. Therefore, we can achieve 5 times higher beam current at the isocenter. However, due to current radiation protection permit allows only 1 nA of maximum beam current through Gantry 2, in scenario C, we derived all the plans by scaling down by a factor 5, the dose per spot and the maximum achievable beam current. Nevertheless, in another study related to FLASH irradiation with PSI's Gantry 1, we already demonstrated that with additional technical measures, it is possible to safely deliver a very high beam current (~680 nA) with our monitoring and control system [26]. Currently, we are in the process to increase the maximum beam current limit for our Gantry 2. After the approval from the local safety authorities, it would be possible to deliver the plans with high-intensity beams.

The transmission improvement studies in this work are however only part of a larger project investigating how beam optics of our cyclotron based proton therapy facilities could be improved in order to optimize beam intensity at isocenter. Indeed, we have already demonstrated that the additional use of asymmetric collimators after the energy degrader (to better select emittance), could gain an additional factor 6 in transmission, thus a factor 30 improvement compared to our current clinical set-up, at least if a 1.5 times increase of the beam size at the isocenter (in air) is acceptable [11]. If such optics could be realized clinically, this would then limit the beam-on times for all fields studies in this work to about one 1 s. Of note, the use of a large beam size could also be of advantage by enabling a further reduction of the number of spots required to cover the target volume, potentially shortening the total delivery time even further. Further treatment planning studies are however required in order to investigate to what extent spot-reduction is affected by increased beam sizes, and whether these plans would be clinically acceptable. Additionally, with a factor of 30 higher beam intensity, we may face problem with the minimum spot delivery duration for some of the spots. However, it could be solved by implementing fast control system using modern electronics. In addition, as beam transmissions and intensities increase, the time for energy layer switching becomes more and more the limiting factor for total delivery time. Additionally then, one could also use a ridge filter to reduce the energy layers required to cover the full target volume. As such, we are currently investigating the possibilities of further reducing delivery time using a novel dynamic ridge filter concept [27,28]. At our institute, we are also developing treatment delivery with line scanning [29] which could also be used as an alternative to spot-reduced treatment planning to reduce the dead time.

In previous studies, it has been shown that breath-hold is well tolerated by patients [4,30,31], with good intrafraction [32] and interfraction [20] reproducibility. Therefore, our study could lead to the use of breath-hold as a preferred motion mitigation technique in a near future. Additionally, the spot-reduced plan were similarly robust against errors in patient setup and proton range to the conventional plan. However, our fast delivery technique is currently at the experimental stage; further investigation of treatment workflow for breath-hold, the selection of right combination of different delivery techniques (such as the use of ridge filter, high-intensity beams, spot-reduced planning, and line scanning) based on the size and shape of the tumor are necessary.

Conclusion

In this proof-of-principle investigation, we have shown that it is possible to achieve conventional fractionated (2 Gy(RBE)/fraction) and hypofractionated (6 Gy(RBE)/fraction) proton therapy within a single breath-hold (5–15 sec) for non-small-cell lung cancers. To this goal, both beam-on time and dead time were improved, using new beam optics in the delivery and spot reduced and optimization in the planning. This is a very promising option to treat moving targets. Additionally, hypofractionation regimes could contribute to reducing the proton therapy treatment cost. This approach therefore could open a wide range of possibilities for both current and future proton therapy practice.

Funding

This work is partially funded by PSI's CROSS funding scheme and EU-H2020 project 'INSPIRE' (INfraStructure in Proton International REsearch; Grant No.: 730983).

Data Availability Statement

The data presented in this article are available upon request from the corresponding authors. The data are not publically available due to sensitive patient information.

Acknowledgement

We would like to acknowledge Mirjana Josipovic and Gitte. F. Persson from Rigshospitalet Copenhagen University Hospital for the DIBH CTs.

Conflicts of Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.06.018.

References

[1] Chang JY, Li H, Zhu XR, Liao Z, Zhao L, Liu A, et al. Clinical implementation of intensity modulated proton therapy for thoracic malignancies. Int J Radiat Oncol Biol Phys 2014;90:809–18. https://doi.org/10.1016/j.ijrobp.2014.07.045.
[2] Pedroni E, Bacher R, Blattmann H, Böhringer T, Coray A, Lomax A, et al. The 200-Mev proton therapy project at the Paul Scherrer Institute: Conceptual design and practical realization. Med Phys 1995;22:37–53. https://doi.org/10.1118/1.597522.
[3] Lin S, Boehringer T, Coray A, Grossmann M, Pedroni E. More than 10 years experience of beam monitoring with the Gantry 1 spot scanning proton therapy facility at PSI. Med Phys 2009;36:5331–40. https://doi.org/10.1118/1.3244034.
[4] Hanley J, Debois MM, Mah D, Mageras GS, Raben A, Rosenzweig K, et al. Deep inspiration breath-hold technique for lung tumors: The potential value of target immobilization and reduced lung density in dose escalation. Int J Radiat Oncol Biol Phys 1999;45:603–11. https://doi.org/10.1016/S0360-3016(99)00154-6.
[5] Dueck J, Knopf A-C, Lomax A, Albertini F, Persson GF, Josipovic M, et al. Robustness of the Voluntary Breath-Hold Approach for the Treatment of Peripheral Lung Tumors Using Hypofractionated Pencil Beam Scanning Proton Therapy. Int J Radiat Oncol Biol Phys 2016;95:534–41. https://doi.org/10.1016/j.ijrobp.2015.11.015.
[6] Mori S, Inaniwa T, Furukawa T, Zenklusen S, Shirai T, Noda K. Effects of a difference in respiratory cycle between treatment planning and irradiation for phase-controlled rescanning and carbon pencil beam scanning. Br J Radiol 2013;86:20130163. https://doi.org/10.1259/bjr.20130163.
[7] Schätti A, Zakova M, Meer D, Lomax AJ. Experimental verification of motion mitigation of discrete proton spot scanning by re-scanning. Phys Med Biol 2013;58:8555–72. https://doi.org/10.1088/0031-9155/58/23/8555.
[8] Ohara K, Okumura T, Akisada M, Inada T, Mori T, Yokota H, et al. Irradiation synchronized with respiration gate. Int J Radiat Oncol Biol Phys 1989;17:853–7. https://doi.org/10.1016/0360-3016(89)90078-3.
[9] Stuschke M, Kaiser A, Pöttgen C, Lübcke W, Farr J. Potentials of robust intensity modulated scanning proton plans for locally advanced lung cancer in comparison to intensity modulated photon plans. Radiother Oncol 2012;104:45–51. https://doi.org/10.1016/j.radonc.2012.03.017.
[10] Gorgisyan J, Munck af Rosenschold P, Perrin R, Persson GF, Josipovic M, Belosi MF, et al. Feasibility of Pencil Beam Scanned Intensity Modulated Proton

Therapy in Breath-hold for Locally Advanced Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2017;99:1121–8. https://doi.org/10.1016/j.ijrobp.2017.08.023.
[11] Maradia V, Meer D, Weber DC, Lomax AJ, Schippers JM, Psoroulas S. A new emittance selection system to maximize beam transmission for low-energy beams in cyclotron-based proton therapy facilities with gantry. Med Phys 2021;48:7613–22. https://doi.org/10.1002/mp.15278.
[12] Maradia V et al. A novel beam optics concept to maximize the transmission through cyclotron-based proton therapy gantries. In: Proc IPAC2021. p. 2477–9. https://doi.org/10.18429/JACoW-IPAC2021-TUPAB407.
[13] Van De Water S, Belosi MF, Albertini F, Winterhalter C, Weber DC, Lomax AJ. Shortening delivery times for intensity-modulated proton therapy by reducing the number of proton spots: An experimental verification. Phys Med Biol 2020;65. https://doi.org/10.1088/1361-6560/ab7e7c.
[14] Maradia V, Giovannelli AC, Meer D, Weber DC, Lomax AJ, Schippers JM, et al. Increase of the transmission and emittance acceptance through a cyclotron-based proton therapy gantry. Med Phys 2022;49:2183–92. https://doi.org/10.1002/mp.15505.
[15] Saito T, Ohnishi K, Ishikawa H, Nakamura M, Hoshiai S, Numajiri H, et al. Hypofractionated Proton Beam Therapy for cT1-2N0M0 Non-small Cell Lung Cancer Patients With Interstitial Lung Disease. Anticancer Res 2021;41:5635–42. https://doi.org/10.21873/anticanres.15379.
[16] Laine AM, Pompos A, Timmerman R, Jiang S, Story MD, Pistenmaa D, et al. The role of hypofractionated radiation therapy with photons, protons, and heavy ions for treating extracranial lesions. Front Oncol 2016;5. https://doi.org/10.3389/fonc.2015.00302.
[17] Shibamoto Y, Miyakawa A, Otsuka S, Iwata H. Radiobiology of hypofractionated stereotactic radiotherapy: What are the optimal fractionation schedules? J Radiat Res 2016;57:i76–82. https://doi.org/10.1093/jrr/rrw015.
[18] Sakaguchi M, Maebayashi T, Aizawa T, Ishibashi N, Fukushima S, Abe O, et al. Patient outcomes of monotherapy with hypofractionated three-dimensional conformal radiation therapy for stage T2 or T3 non-small cell lung cancer: A retrospective study. Radiat Oncol 2016;11. https://doi.org/10.1186/s13014-016-0582-1.
[19] Nenoff L, Ribeiro CO, Matter M, Hafner L, Josipovic M, Langendijk JA, et al. Deformable image registration uncertainty for inter-fractional dose accumulation of lung cancer proton therapy. Radiother Oncol 2020;147:178–85. https://doi.org/10.1016/j.radonc.2020.04.046.
[20] Josipovic M, Persson GF, Dueck J, Bangsgaard JP, Westman G, Specht L, et al. Geometric uncertainties in voluntary deep inspiration breath hold radiotherapy for locally advanced lung cancer. Radiother Oncol 2016;118:510–4. https://doi.org/10.1016/j.radonc.2015.11.004.
[21] Lomax A. Intensity modulation methods for proton radiotherapy. Phys Med Biol 1999;44:185–205. https://doi.org/10.1088/0031-9155/44/1/014.
[22] Lomax AJ, Böhringer T, Bolsi A, Coray D, Emert F, Goitein G, et al. Treatment planning and verification of proton therapy using spot scanning: Initial experiences. Med Phys 2004;31:3150–7. https://doi.org/10.1118/1.1779371.
[23] Safai S, Bula C, Meer D, Pedroni E. Improving the precision and performance of proton pencil beam scanning. Translat Cancer Res 2012. https://doi.org/10.3978/j.issn.2218-676X.2012.10.08.
[24] Wieser H-P, Cisternas E, Wahl N, Ulrich S, Stadler A, Mescher H, et al. Development of the open-source dose calculation and optimization toolkit matRad. Med Phys 2017;44:2556–68. https://doi.org/10.1002/mp.12251.
[25] Breedveld S, Storchi PRM, Voet PWJ, Heijmen BJM. ICycle: Integrated, multicriterial beam angle, and profile optimization for generation of coplanar and noncoplanar IMRT plans. Med Phys 2012;39:951–63. https://doi.org/10.1118/1.3676689.
[26] Nesteruk KP, Togno M, Grossmann M, Lomax AJ, Weber DC, Schippers JM, et al. Commissioning of a clinical pencil beam scanning proton therapy unit for ultra-high dose rates (FLASH). Med Phys 2021;48:4017–26. https://doi.org/10.1002/mp.14933.
[27] Maradia V et al. Universal and dynamic ridge filter for pencil beam scanning (PBS) proton therapy Vivek Maradia Paul Scherrer Institute Universal and dynamic ridge filter for pencil beam scanning (PBS) proton therapy. Radiother Oncol 2022. https://doi.org/10.3929/ethz-b-000545919.
[28] Maradia V et al. Universal and dynamic ridge filter for pencil beam scanning (PBS) proton therapy Vivek Maradia Paul Scherrer Institute Universal and dynamic ridge filter for pencil beam scanning (PBS) proton therapy. Radiother Oncol 2022;170:S549–50. https://doi.org/10.1016/S0167-8140(22)02644-5.
[29] Klimpki G, Psoroulas S, Bula C, Rechsteiner U, Eichin M, Weber DC, et al. A beam monitoring and validation system for continuous line scanning in proton therapy. Phys Med Biol 2017;62:6126–43. https://doi.org/10.1088/1361-6560/aa772e.
[30] Panakis N, McNair HA, Christian JA, Mendes R, Symonds-Tayler JRN, Knowles C, et al. Defining the margins in the radical radiotherapy of non-small cell lung cancer (NSCLC) with active breathing control (ABC) and the effect on physical lung parameters. Radiother Oncol 2008;87:65–73. https://doi.org/10.1016/j.radonc.2007.12.012.
[31] Josipovic M, Persson GF, Håkansson K, Damkjær SMS, Bangsgaard JP, Westman G, et al. Deep inspiration breath hold radiotherapy for locally advanced lung cancer: Comparison of different treatment techniques on target coverage, lung dose and treatment delivery time. Acta Oncol (Madr) 2013;52:1582–6. https://doi.org/10.3109/0284186X.2013.813644.
[32] Scherman Rydhög J, Riisgaard de Blanck S, Josipovic M, Irming Jølck R, Larsen KR, Clementsen P, et al. Target position uncertainty during visually guided deep-inspiration breath-hold radiotherapy in locally advanced lung cancer. Radiother Oncol 2017;123:78–84. https://doi.org/10.1016/j.radonc.2017.02.003.