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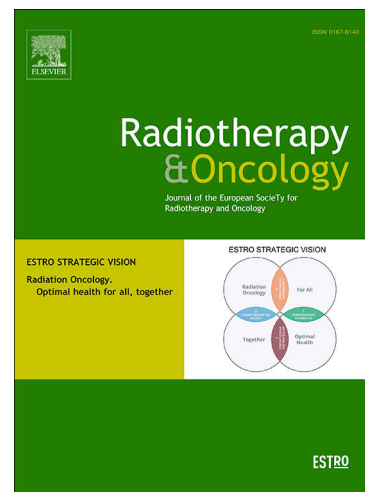
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# Ultra-fast pencil beam scanning proton therapy for locally advanced non-small-cell lung cancers: field delivery within a single breath-hold

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## Keywords:

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

## Highlight:

- PBS proton therapy within a single breath-hold (15 sec)
- Hypofractionation within a single breath-hold
- Treatment of moving targets

**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.

**Introduction**

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 10-16s [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 addition 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 x 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.

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).

Patient number	NSCLC stage	Tumor volume			Target location	PSI plan		Spot Reduced Plan	
		GTV (cm <sup>3</sup> )	CTV (cm <sup>3</sup> )	PTV (cm <sup>3</sup> )		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	10945	103	824
3	T4N3	50	94	186	Right Lobe	142	14060	139	1163
4	TXN3M0	37	114	205	Right Lobe	126	16394	124	1559
5	T3N0M0	88	162	267	Right Lobe	111	17909	109	1107
6	T2BN2M0	63	158	276	Right Lobe	117	13522	116	820
7	T4N2	54	161	307	Left Lobe	201	15279	195	1041
8	T4N2M0	78	165	310	Right Lobe	150	19926	147	965
9	T2BN3M0	107	202	368	Left Lobe	244	21756	240	1743
10	T4N2M0	105	220	379	Left Lobe	151	23427	147	1786

## (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 0.5<sup>th</sup> 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, Figure 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.

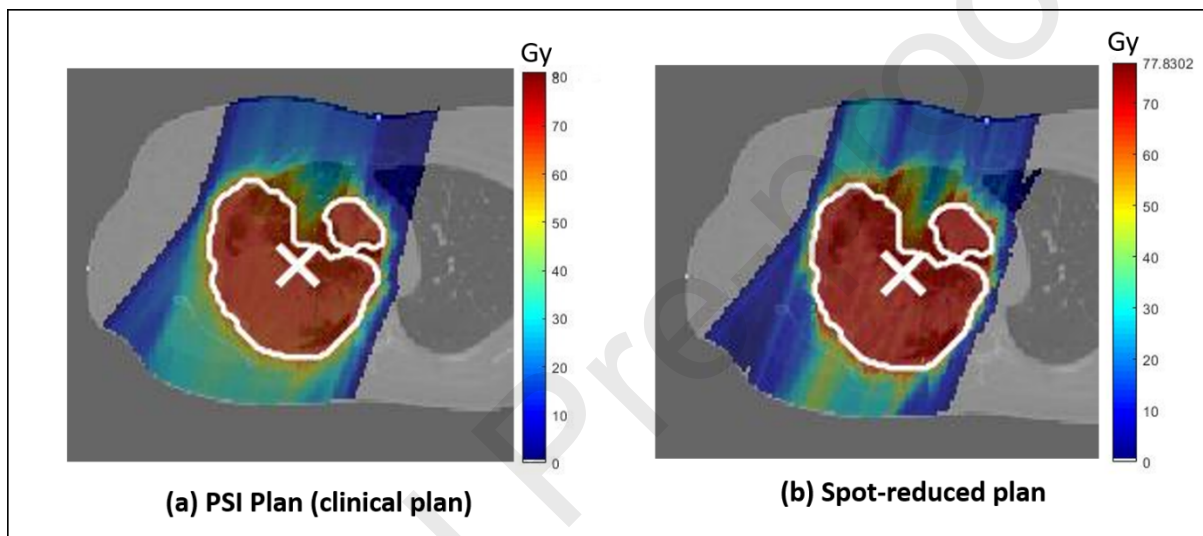


Figure 1 Total dose distribution of lung case number 10 (PTV: 379 cm<sup>3</sup>) with (a) PSI plan (clinical plan) and (b) spot-reduced plan

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.

Lung case #	Planning target volume (PTV) dose parameters								Dose in OAR (Mean dose (%))					
	Mean dose (%)		V <sub>95%</sub> (%)		D <sub>2%</sub> (%)		HI (D <sub>5</sub> /D <sub>95</sub> )		Dose in lung		Dose in heart		Dose in medulla	
	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	

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  $\pm 5\%$  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

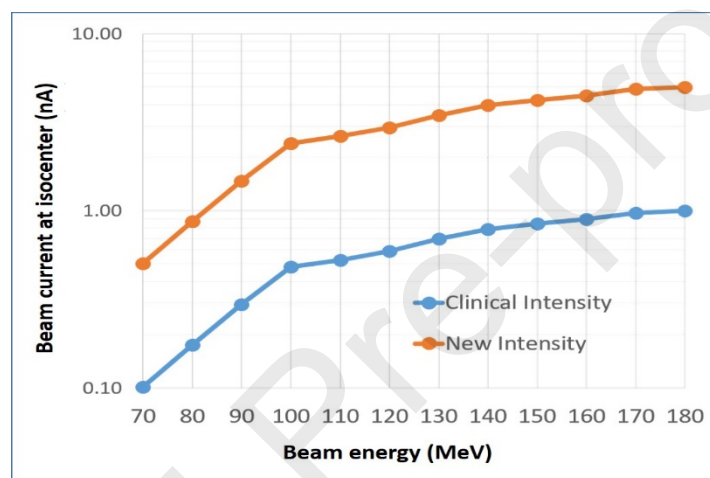


Figure 2 Comparison of beam current at isocenter for different energy beams. Beam current is normalized for clinical beam intensity.

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 (Figure 2). Through this optimization process, a factor 5 higher transmission efficiency could be achieved for all proton energies (Figure 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 figure 2. As beam-on time and dose scale linearly, by this 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 figure 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.

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

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.

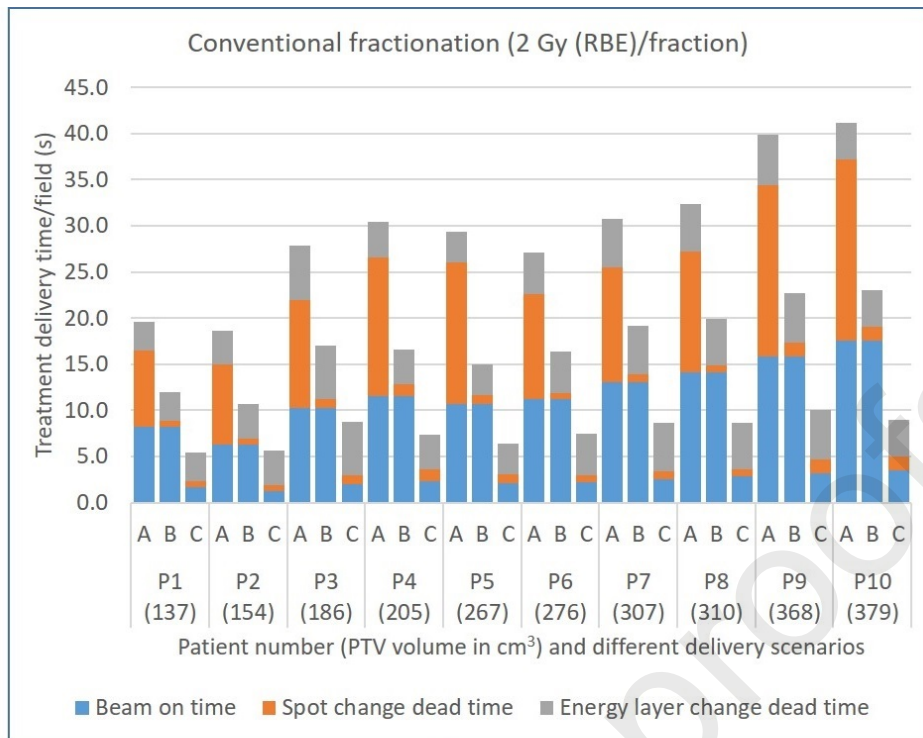
### Results

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  $\pm 1$  second of each other. Therefore, for simplicity, we report the field delivery time of only one field (field-1) for each patient case.

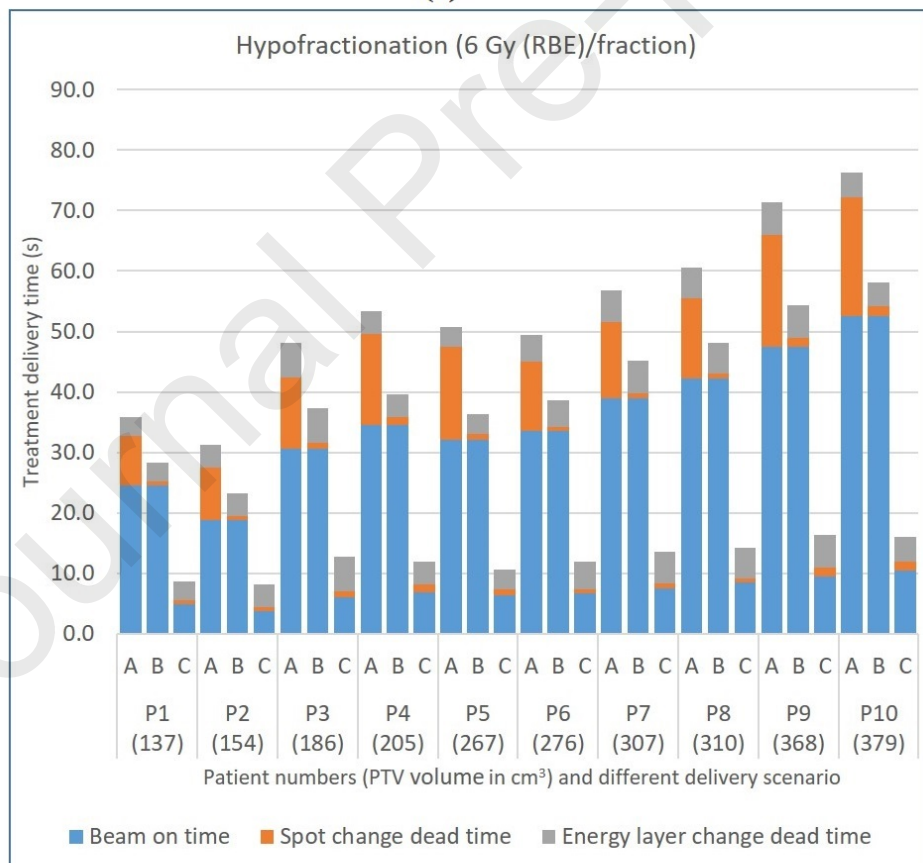


To investigate the feasibility of conventional fractionation proton therapy within a single breath-hold, we also delivered all scenarios with 2 Gy(RBE)/fraction. For scenario A, and as can be seen from Figure 3(a), the total delivery time per field for all cases (independent of tumor size and shape) 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 10s, even for the largest tumor. As such, we reduce delivery time by about 74% ( $\pm 3.3\%$  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 (Figure 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  $\sim 77\%$  ( $\pm 1.9\%$ ) (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 15s, which is still of the order of the expected breath-hold duration for lung cancer patients [4].



(a)



(b)

Figure 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

## 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 to 379 cm<sup>3</sup>), 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 5-15s 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).

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 1s. 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.

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## **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.

### Conflicts of Interest

The authors declare no conflict of interest.

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Journal Pre-proofs

There is no conflict of interest

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