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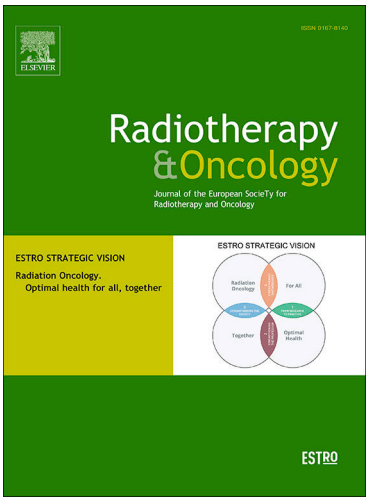

Original Article

The impact of organ motion and the appliance of mitigation strategies on the effectiveness of hypoxia-guided proton therapy for non-small cell lung cancer

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The impact of organ motion and the appliance of mitigation strategies on the effectiveness of hypoxia-guided proton therapy for non-small cell lung cancer

Short running title: Motion in hypoxia-guided proton therapy

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The impact of organ motion and the appliance of mitigation strategies on the effectiveness of hypoxia-guided proton therapy for non-small cell lung cancer

0. Abstract

Background and Purpose: To investigate the impact of organ motion on hypoxia-guided proton therapy treatments for non-small cell lung cancer (NSCLC) patients.

Materials and Methods: Hypoxia PET and 4D imaging data of six NSCLC patients were used to simulate hypoxia-guided proton therapy with different motion mitigation strategies including rescanning, breath-hold, respiratory gating and tumour tracking. Motion-induced dose degradation was estimated for treatment plans with dose painting of hypoxic tumour sub-volumes at escalated dose levels. Tumour control probability (TCP) and dosimetry indices were assessed to weigh the clinical benefit of dose escalation and motion mitigation. In addition, the difference in normal tissue complication probability (NTCP) between escalated proton and photon VMAT treatments have been assessed.

Results: Motion-induced dose degradation was found for target coverage (CTV $V_{95\%}$ up to -4%) and quality of the dose-escalation-by-contour (Q_{RMS} up to 6%) as a function of motion amplitude and amount of dose escalation. The TCP benefit coming from dose escalation (+4-13%) outweighs the motion-induced losses (<2%). Significant average NTCP reductions of dose-escalated proton plans were found for lungs (-14%), oesophagus (-10%) and heart (-16%) compared to conventional VMAT plans. The best plan dosimetry was obtained with breath hold and respiratory gating with rescanning.

Conclusion: NSCLC affected by hypoxia appears to be a prime target for proton therapy which, by dose-escalation, allows to mitigate hypoxia-induced radio-resistance despite the sensitivity to organ motion. Furthermore, substantial reduction in normal tissue toxicity can be expected compared to conventional VMAT. Accessibility and standardization of hypoxia imaging and clinical trials are necessary to confirm these findings in a clinical setting.

2. Introduction

Tumour hypoxia refers to a state in which tumour cells are exposed to abnormally low levels of oxygen. This is thought to be primarily induced by insufficient blood supply in the tumour resulting from a dysfunctional tumour vasculature originating from the unregulated and chaotic growth of the tumour cells[1,2]. Hypoxia has been associated to a decreased effectiveness of radiotherapy treatments in non-small cell lung cancer (NSCLC)[3,4], making hypoxia-targeted therapies an attractive therapeutic option[5,6]. Pencil-beam scanning (PBS) proton therapy could prove to be an interesting treatment modality in this context. PBS has the intrinsic capability of dose painting and reduction of the integral dose, decreasing the burden to normal tissues. The benefit of dose escalation with proton therapy to target radio-resistance in lung cancer has been shown in comparative planning studies, simulating treatment in stationary anatomy conditions[7,8]. The dose degradation due to organ motion observed with protons may however jeopardize the hypothesized benefits of improved treatment conformity.

Efforts towards the integration of 4D-imaging in the planning process together with the clinical translation of motion mitigation strategies into proton therapy[9,10] have enabled the treatment of targets subject to organ motion. Robust treatment planning[11], rescanning[12] or motion mitigation in the form of breath-hold[13] or respiratory gating[9] are already well-established and developments in the field of tumour tracking[14,15] may allow to control organ motion without a need for significantly increased margins. Dose painting strategies such as dedicated escalation to target tumour hypoxia require careful evaluation in that context, given that the prescription of different dose levels to the target area could be particularly sensitive to motion-induced degradation.

The aim of this study was to weigh the decrease in proton treatment effectiveness caused by organ motion against the potential benefits of a hypoxia-targeted dose escalation in NSCLC patients. We evaluated dose degradation and losses in target coverage induced by organ motion for different motion mitigation strategies, including strategies that are commonly applied in proton therapy and tumour tracking, which although not clinically available for protons, can be considered the most advanced technique in photon therapy[16]. Benefits in terms of tumour control probability (TCP) from a hypoxia-targeted dose escalation strategy were compared against losses caused by the organ motion. The findings were complemented with normal tissue complication probability (NTCP) estimations to determine the most suitable motion mitigation strategy to target hypoxia in NSCLC with proton therapy and benchmark these against state-of-the-art volumetric intensity modulated arc (VMAT) photon treatments.

3. Materials and Methods

3.A. Patient data and treatment planning

Treatments were simulated for six stage IIb-IIIb non-small cell lung cancer (NSCLC) patients included in an ongoing phase II randomised clinical trial (NCT01024829) for PET-guided dose escalation[8,17] with photons. The available imaging and planning data for all patients included a 4D CT with eight breathing phases, a mid-position CT with target and organ at risk (OAR) structures as well as an HX4 hypoxia PET image. Motion amplitudes of the gross tumour volume (GTV) were in the range of 2-23 mm (median, 11.8) and median partial oxygen pressure (pO_2) values in the hypoxic-subvolumes were between 5.3 and 10.6 mmHg. The hypoxic subvolumes were defined according to Köthe et al.[8], as the regions with normalised PET standardised uptake above 1.4. Dose escalation levels were determined by quantifying physical pO_2 levels from the hypoxia images and a proton-specific parametrization of the oxygen enhancement ratio (OER) that takes dose-averaged LET distributions into account[18]. OER values in the hypoxic sub-volume were averaged to obtain the patient-specific level of dose escalation[8]. Detailed patient characteristics are summarised in table 1.

For our planning study, for each patient, five treatment plans were prepared: one VMAT photon breath-hold (BH) treatment with homogeneous dose prescription and four PBS proton therapy plans with dose escalation on the hypoxic subvolumes for different motion scenarios simulating BH, free-breathing (FB), tumour tracking (TRK) and gating (GAT) treatments. Free-breathing and tracking plans were optimized on the mid-position image [19] created from the 4D CT series (Velocity version 4.1, Varian Medical Systems, Palo Alto, CA, USA). Since the

available 4D CT covered only the regular free breathing range of the patients with no deep inspiration anatomy available, for breath-hold treatments, the single end-expiratory phase was used, which is the closest representation of the anatomy of deep exhalation [20] that we have in our data set. The gating window was similarly centered on end-exhale and its width defined to keep the residual motion below 5 mm. A planning mid-position CT was generated from the 4D CT phases within the window. The planning constraints were set according to the RTOG 1308 trial[21] (NCT01993810), with a prescription dose of 70 Gy_{RBE} (RBE: Relative biological effectiveness) to the PTV (2 Gy_{RBE}/fraction). The option to override the ITV density for planning purposes was not explored. The dose escalation was implemented as a simultaneous integrated boost 'by contour' adapted to each individual patient hypoxia level[8] (see table 1).

Margins were adapted to the treatment modality, amplitude of motion and motion management technique. Internal target volumes (ITVs), defined as the union of GTVs across the relevant breathing phases, were employed in the free-breathing and gating scenarios. The ITV_{GTV} was expanded by 5 mm to form the clinical target volume (CTV)[17,22]. Isotropic 5 mm CTV-to-PTV margins were considered for the lymph nodes, whereas primary target margins were determined as follows[23,24]:

$$Margin_{CTVtoPTV}[mm] = 2.5\Sigma + \sqrt{\sigma^2 + 0.125A^2}$$

where Σ and σ represent the systematic and random uncertainties and A the motion amplitude. The contribution of systematic errors for protons was assumed to be larger (2 mm) than for photons (1 mm) given the different shape of the respective depth-dose curves and were based on previous uncertainty estimations from our institute[25]. The random component was set at 3 mm for both modalities. This resulted in a 5 mm CTV-to-PTV margin for photon plans and 7-11 mm margins for the proton ones, taking into account all forms of uncertainty. Further details can be found in supplement S3.

VMAT plans were optimized with RapidArc (Eclipse version 16, Varian Medical Systems, Palo Alto, CA, USA) based on 6 MV Varian True beam machine data. Full arcs were employed for medial tumours, half arcs for the more lateral ones. Three-field proton plans favoring anterior and posterior beam directions were optimized in single field optimization (SFO) with an in-house developed treatment planning system[26]. Linear energy transfer (LET) calculations were performed for the proton plans based on dose-averaged LET (LET_d). An RBE of 1.1 was assumed throughout the entire study.

While for proton and photon breath-hold plans, a static anatomy was assumed, 4D dose calculation was performed for all other treatment scenarios[14,15], including PBS volumetric rescanning. Overall, 14 treatment scenarios were simulated for each patient: a photon plan, a static reference proton plan for each motion mitigation technique (BH, FB, TRK, GAT) and three 4D plans for FB, TRK and GAT, with 1, 2 and 4 rescans (RS). In accordance with the capabilities of our facility, rescanning with up to 4 RS could be performed without being constraint by a minimum MU requirement per spot. For all scenarios, a single fraction was simulated and assumed to be representative for the entire treatment course, thus ignoring the beneficial averaging effect of daily random uncertainties.

More detailed information regarding the planning procedures and 4D dose calculation can be found in the supplementary material.

3.B Treatment plan evaluation

Plan robustness against motion-induced degradations were evaluated through the usage of dedicated plan evaluation metrics. Target coverage was evaluated through CTV $V_{95\%}$ and homogeneity index (HI) of the dose escalation volume[27]:

$$HI = \frac{D_5 - D_{95}}{D_{prescr} \cdot DE}$$

With a prescription dose D_{prescr} of 70 Gy_{RBE} and the dose escalation ratio *DE*. Finally, the quality of the dose distribution was evaluated based on the root mean squared deviation Q_{RMS} from the quality value $Q(\vec{x}) = \frac{D_{4D}(\vec{x})}{D_{static}(\vec{x})}$ defined as[28]:

$$Q_{RMS} = \sqrt{\frac{1}{n}\sum_{CTV}(Q(\vec{x}) - 1))^2}$$

In addition to these target metrics, the TCP in the CTV was estimated with a generalised equivalent uniform dose[29] (EUD) model based on a parametrisation from the Okunieff report[30] for a multi-institutional cohort of NSCLC patients. The volume parameter *a* for the EUD, calculated as $EUD = \left(\sum_i v_i {D_i}^a\right)^{\frac{1}{a}}$ with D_i the i-th dose bin of the differential dose-volume histogram and v_i the associated relative volume, was set to -10[31] .The biologically effective dose in each voxel, obtained through the use of the OER[18], was considered for TCP calculations. Individual voxel OER was calculated from LET_d and pO_2, the latter quantified from the standard uptake values (SUV) of the HX4 PET image[32].

Lung volume excluding GTV, heart, oesophagus and spinal cord were considered organs-at-risk (OARs). Dose comparisons in terms of normal tissue toxicity between photon and proton plans were performed by comparing the best-case photon scenario treating a static anatomy without dose escalation to the worst-case proton scenario of a treatment under the condition of organ motion, without rescanning and including dose escalation. In addition to conventional DVH parameters for these organs, NTCP estimations were performed according to the Dutch thoracic model-based approach[33] including adjusted and validated NTCP models for radiation pneumonitis (grade $\geqslant$ 2)[34], acute esophageal toxicity (grade $\geqslant$ 2)[35,36] and 2-year mortality[37] based on heart dose. Details about these models as well as patient parameters can be found in the supplementary material S1. All evaluations were performed in MATLAB (2020b, The MathWorks, Natick, MA, USA).

4. Results

Proton dose degradations were shown to be amplified in patients with large organ motion treated with a low number of rescans (Figure 1). Some illustrative dose distributions, showing overshoots and interplay effects, are provided in the supplementary material S2. $V_{95\%}$ in the CTV, a surrogate for target coverage, dropped by a maximum of 4% for the FB, 3% for the TRK, and 1% for the GAT plans compared to the static reference plans ($V_{95\%}$ = 100%). Losses in $V_{95\%}$ were most severe in the FB treatments, followed by TRK and GAT with rescanning improving coverage in all cases, reducing losses in $V_{95\%}$ to maximally 2.5%. Coverage was maintained in BH treatments, as those cases were treated as a stationary geometry.

Dose homogeneity differences in the hypoxic sub-volumes were as high as 15% for patients with the largest dose escalation (patients 04 and 01) compared to the static plan where an HI of 2-3% was achieved. Homogeneity in the hypoxic sub-area was best preserved in gated treatments, followed by tracking and free-breathing with higher rescanning factors improving homogeneity (up to 8% for FB in patient 04).

Finally, Q_{RMS} allows an assessment of the overall quality of the dose distribution with respect to the planned one. Again, higher amplitude of motion was associated with a lower treatment quality with an improvement through the usage of rescanning. With a maximal uncertainty of 6% in Q_{RMS}, FB treatments were the most susceptible to dose uncertainties introduced by organ motion. GAT showed the lowest amount of dose degradation with a relatively consistent Q_{RMS} between 0.9% and 2.8% (Figure 1). Overall, while observing a clear correlation between motion amplitude and motion-induced degradations, particularly visible in a large decrease in dose homogeneity, treatments plans were relatively robust against motion-induced dose distortions with reductions of target coverage and quality of the dose distribution well below 10%.

Figure 2 summarises the impact of hypoxia and motion on TCP relative to the static dose escalation plans, where the TCP was estimated to be around 75%. In absence of dose escalation, hypoxia-induced losses of TCP between 4% and 13% (mean, 7.5%) were observed as a function of the individual patient condition. In comparison, motion-induced losses in TCP were below 2% for all simulated scenarios. The highest amount of TCP reduction (1-2%) was observed for patients with larger motion (> 15 mm, 04 and 05) and the most severe hypoxia (< 6 mmHg, 04 and 01). Patients with little motion (02, 03, and 06) did not show motion-induced TCP degradation (<0.5%). Rescanning, although being a minor contribution, showed benefits for the TCP. Overall, in terms of TCP the benefit of dose escalation, ranging from 4% to 13% (mean, 7.5%) outweighed the motion-induced losses (< 2%).

Despite the escalated dose levels of the proton plans and effects of organ motion, doses for all organs at risk were reduced with respect to conventional VMAT photon plans. Mean doses in the lungs, heart and oesophagus dropped on average by 8.2 Gy_{RBE} (max 9.9), 15.5 Gy_{RBE} (max 25.7) and 8.8 Gy_{RBE} (max 10.6) respectively. $D_{2\%}$ in the oesophagus could be reduced by 12.6 Gy_{RBE} and the maximum dose in the spinal cord by 22.5 Gy_{RBE} on average. Dosimetric benefits from proton plans were prominent in the low dose regions.

The NTCPs based on these doses are summarised in figure 3. Compared to the photon scenario and despite escalated dose levels to the target, all patients showed reduced NTCP in lungs and heart and, for most patients, in the oesophagus (83%). The risk for radiation pneumonitis (RP) was on average decreased by 13.7%, for acute esophagitis by 10.3% and importantly for (heart dose-driven) 2-year mortality by 15.7%. Such an improvement in expected toxicity was found to be only marginally affected by organ motion (<1%). In addition, while the increased margins considered to plan FB treatments have led to an increase in the risk for RP of up to 6% compared to motion mitigated scenarios, the other endpoints were not affected by the choice of the motion mitigation technique (<1%).

5. Discussion

We found that motion-induced dose degradations affect target coverage and the quality of the hypoxia-targeted dose-escalation-by-contour for NSCLC patients as a function of motion amplitude and amount of dose escalation. However, TCP benefits from dose escalation outweigh motion-induced TCP losses (Fig. 2). Furthermore, large dosimetric benefits for OARs as well as NTCP reductions could be found for proton treatments compared to conventional, non-escalated photon plans. Our findings suggest that targeting hypoxia with proton therapy in large NSCLC tumours can be largely beneficial despite the protons' sensitivity to organ motion. Based on our simulations considering a PTV-based planning strategy and various motion mitigation techniques, gating combined with rescanning, at the cost of extended treatment time, offers the greatest potential to maximize the benefits of this dose escalation strategy based on proton therapy, should motion mitigation be necessary.

Combining a variety of treatment modalities and dose response models introduces uncertainty. The calibration of HX4 image intensity to pO_2[32] and subsequently OER[18] has not been extensively studied or clinically validated. The TCP model, despite being built on multi-institutional data, has not been validated in an independent cohort and the NTCP models, while being externally validated, purely depend on the mean dose of the OARs, which has been questioned in other studies[38,39]. Finally, different deformable image registration algorithms have been shown to lead to different results when used for dose accumulation[40,41]. Despite these uncertainties, we argue that the general trends outlined in our study remain valid. First, not only the NTCPs, but also the doses to the OARs were substantially lower in all proton plans. Second, OER values of 1.1-1.2 are not unreasonable based on in-vitro cell experiments[18,42]. This implies that, in the absence of dose escalation, the biologically effective dose in the entire hypoxic compartment, reduced by 10-20% compared to the normoxic conditions, is arguably more relevant than localized motion-induced underdosage of a few percent. Overall, while the resulting absolute TCP and NTCP estimations are affected by a certain degree of uncertainty, the differences with regards to the photon or static plans are expected to have general validity.

Our hypoxia simulations have been carried out under the assumption that PET images taken at the planning stage remain stable throughout the entire treatment. This is unlikely to represent a realistic clinical scenario due to the radiation affecting the tumour microenvironment and reoxygenation taking place[3,43]. The temporal evolution of hypoxia throughout the treatment has not been studied extensively, but several studies report

noticeable changes or even complete reoxygenation after some fractions[44,45]. Indeed, our simulations could be regarded as a worst-case scenario, since an intensification of hypoxia during the treatment is unlikely. The effect of hypoxia could therefore have been overestimated in our simulations with patient-specific dose escalation prescriptions being higher than necessary. Despite that, the NTCP benefit was benchmarked against homogeneous photon doses and remains valid in this worst-case scenario. Further investigations would benefit from hypoxia information obtained at multiple time-points throughout the course of treatment.

Additionally, we would like to point out that due to the difficulty of obtaining 4D-resolved imaging paired with functional hypoxia data for NSCLC patients, this study has been conducted on 6 patients only. Despite the low number of patients, the investigated cases cover a large variety of scenarios regarding tumour size, position, magnitude of motion (1-23 mm) and hypoxia. In all 6 cases, a hypoxia-targeted dose escalation with protons showed benefits in terms of TCP and NTCP, even under consideration of motion. This suggests that the findings may also remain valid in larger datasets.

Another aspect to discuss is the fact that treatment plans were not optimized to minimize NTCPs, but to adhere to the RTOG planning constraints[21]. This might have exaggerated the estimated benefit of proton treatments for 2-year mortality since in order to fulfill constraints for the lung (in particular $V_{5Gy} < 60\%$), doses to the heart were increased in certain VMAT plans, resulting in a higher risk for mortality. While it is possible to minimize NTCP differences between proton and photon treatments by optimizing mean doses to the OARs only, large NTCP deltas are expected to remain due to the increased integral photon dose.

Despite the substantial clinical research efforts from the last decade, it has to be acknowledged that treatments for extracranial tumors affected by respiration-induced organ motion are currently lacking standard operation procedures with a wide consensus. Our treatment planning approach was based on a PTV concept, using statistical margins to take uncertainties (range, positioning, etc.) into account. Alternatively, robust optimization has been proposed to improve indeed plan robustness against motion. Any planning approach resulting in treatment plans that are less sensitive to degradation due to organ motion can only reinforce our conclusion, i.e. that the benefits of dose escalation outweigh motion-induced degradation. In this study, the use of a canonical PTV-based planning approach, has in some cases required resource-intensive techniques, involving e.g. high scanning regimes, which put a strain on the performance of commercial treatment units. Robust planning could instead reduce the role of active motion mitigation techniques, such as gating, tracking or rescanning, and their necessity to recoup the benefit of the proposed dose escalation in the management of extracranial patients. Moreover, the dose averaging effect from treatment fractionation further reduces the impact of organ motion on dose distortions and, in turn, the need of active motion mitigation at treatment time. 4D imaging at multiple time-points during the treatment course is however not available to us, and therefore we presented a worst-case scenario from single-fraction simulations.

We simulated a range of motion mitigation techniques in the context of hypoxia-guided proton therapy of lung cancer. Based on our simulations from the available data, we would recommend the following considerations: the amplitude of motion is the main cause of

impaired target coverage in proton treatments (fig. 1), directly followed by the level of dose escalation. Consequently, should motion mitigation be necessary to ensure treatment conformity, our results from PTV-based planning suggest that respiratory gating is recommended for a motion amplitude exceeding 5 mm, outperforming free-breathing and tracking scenarios. In addition, under the condition of possible patient compliance, breath hold could present an interesting option, which warrants further investigation into the reproducibility and inter-breath hold variability of this technique. In agreement with published results[12,46], rescanning is beneficial in all simulated scenarios and recommended wherever technically possible.

In conclusion, the benefit of targeting hypoxia with dose-escalation-by-contour proton therapy outweighs dose distortions due to respiratory organ motion. In addition, large NTCP benefits for all organ-at-risks were observed compared to conventional VMAT, despite escalated dose levels. With advances in hypoxia imaging, anticipating better reproducibility and accessibility, advanced stage NSCLC presents a prime target for the application of proton therapy. Clinical trials are therefore warranted to provide evidence that the in-silico benefits can be safely translated into a clinical setting.

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Captions

Table 1: Patient characteristics. Abbreviations: pO_2: partial oxygen pressure, AP: anterior-posterior, LR: left-right, SI: superior-inferior

Figure 1: Overview of target dose metrics to evaluate the coverage under consideration of organ motion for all patients and motion mitigation techniques. All metrics are evaluated with respect to the static plan (Δ). Rescanning (RS) improves all target metrics regardless of the specific motion mitigation technique in use. Larger motion amplitude and higher amount of dose escalation are associated to lower coverage (CTV_{V95}), dose homogeneity ($HI_{Hypoxic}$) inside the hypoxic sub-volume and quality of the dose distribution (Q_{RMS}). Grayed out areas represent scenarios where gating was not applicable due to the motion amplitude not exceed 5 mm. Abbreviations: BH: Breath-hold, FB: Free-breathing, TRK: Tracking, GAT: Gating, RS: Rescans

Figure 2: TCP estimations for all patients and 4D scenarios. Without dose escalation (standard plan), hypoxia-induced losses in TCP can reach up to 13% which can be mitigated to within 2% of the planned TCP by dose escalation in any motion scenario. The degree of hypoxia for each patient is represented by the grey curve and is directly correlated to the degree of TCP reduction.

Figure 3: NTCP benefits of dose-escalated proton treatments under consideration of motion compared to photon VMAT for radiation pneumonitis (a), acute esophagitis (b) and 2-year mortality (c). All proton treatments show benefits for heart and lungs and most for the oesophagus. NTCP estimations are not affected by motion.

Highlights

- We investigated the impact of organ motion on the effectiveness of hypoxia-guided proton therapy in lung cancer patients
- Large motion amplitude, especially together with increased dose escalation, was associated with a reduction of target coverage and dose homogeneity
- TCP benefits from dose escalation outweigh motion-induced TCP losses

- Large NTCP benefits for lungs, heart and oesophagus were found for escalated proton plans, even compared to photon plans.
- Respiratory gating in combination with rescanning is the recommended strategy should motion mitigation be necessary

Keywords
Proton therapy, NSCLC, hypoxia, PET, TCP, NTCP, VMAT, Motion, Dose escalation, 4D

Table 2: Patient characteristics. Abbreviations: pO_2: partial oxygen pressure, AP: anterior-posterior, LR: left-right, SI: superior-inferior

Patient ID	Age [years]	Sex	Tumor Stage (UICC)	GTV Volume [cc]	Hypoxic Volume [cc]	Median pO_2 [mmHg] in hypoxic sub-volume	Dose escalation [%]	Motion [mm] AP	Motion [mm] LR	Motion [mm] SI	Motion phases in gating window [%]
01	66	M	IIIb	95.2	48.3	5.3	17	1.4	7.3	12.6	37.5
02	46	F	IIIa	191.1	58.9	6.2	15	1.2	2.4	2.8	100
03	65	F	IIIa	86	8.0	7.6	12	2.6	1.7	11	62.5
04	66	M	IIIa	107.4	52	5.3	22	3.8	3	23.2	25
05	77	M	IIIa	304.9	20.9	7.0	13	0.9	5.3	17.2	37.5
06	82	M	IIb	63.3	5.2	10.6	12	0.4	1.3	1.6	100

Conflicts of Interest
None

Figure 1

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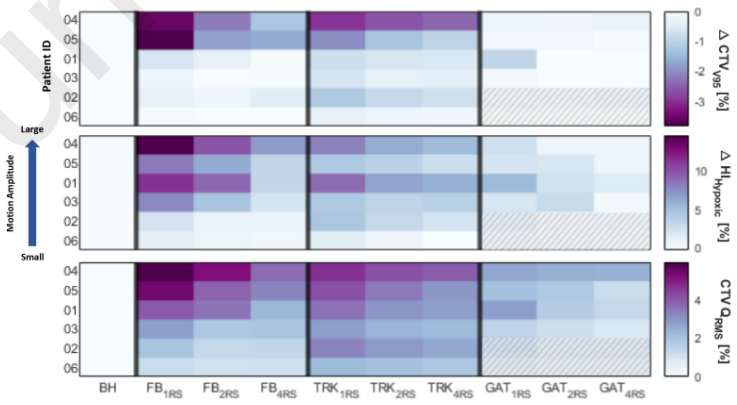

Figure 2

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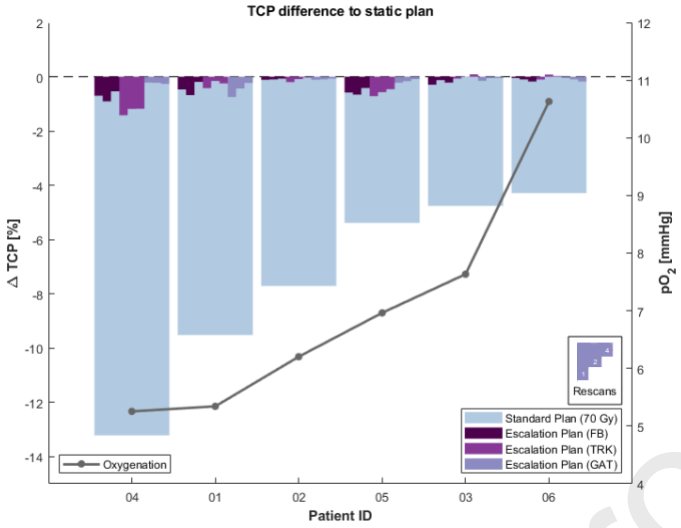

Figure 3a

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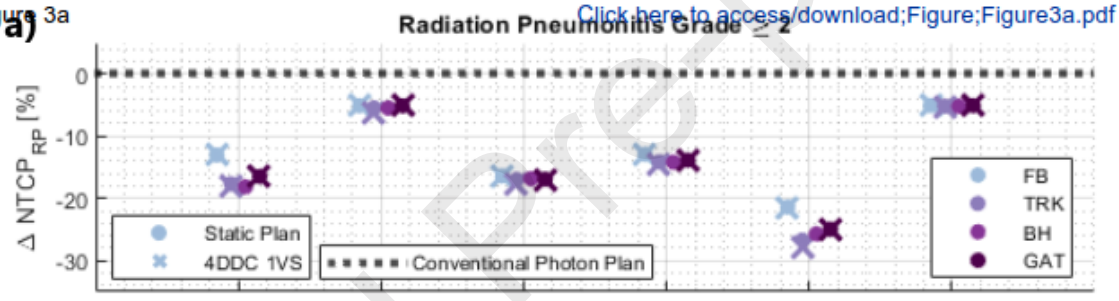

Figure 3b

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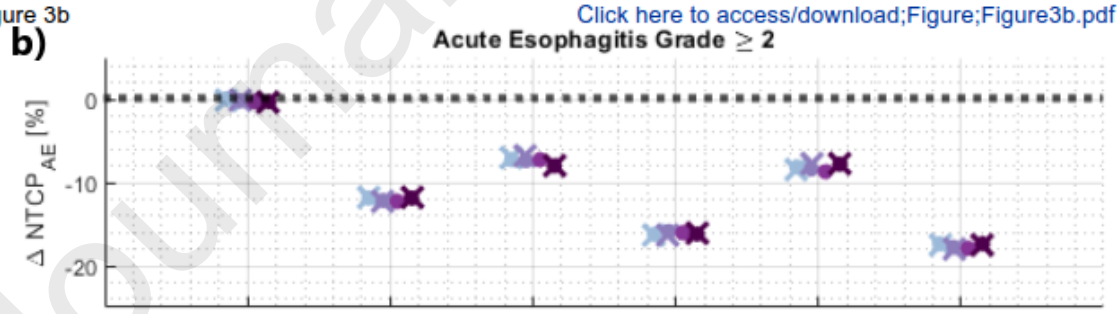

Figure 3c

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