The influence of patient positioning uncertainties in proton radiotherapy on proton range and dose distributions

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(Received 28 February 2014; revised 24 July 2014; accepted for publication 27 July 2014; published 26 August 2014)

Purpose: Proton radiotherapy allows radiation treatment delivery with high dose gradients. The nature of such dose distributions increases the influence of patient positioning uncertainties on their fidelity when compared to photon radiotherapy. The present work quantitatively analyzes the influence of setup uncertainties on proton range and dose distributions.

Methods: Thirty-eight clinical passive scattering treatment fields for small lesions in the head were studied. Dose distributions for shifted and rotated patient positions were Monte Carlo-simulated. Proton range uncertainties at the 50%- and 90%-dose falloff position were calculated considering 18 arbitrary combinations of maximal patient position shifts and rotations for two patient positioning methods. Normal tissue complication probabilities (NTCPs), equivalent uniform doses (EUDs), and tumor control probabilities (TCPs) were studied for organs at risk (OARs) and target volumes of eight patients.

Results: The authors identified a median 1σ proton range uncertainty at the 50%-dose falloff of 2.8 mm for anatomy-based patient positioning and 1.6 mm for fiducial-based patient positioning as well as 7.2 and 5.8 mm for the 90%-dose falloff position, respectively. These range uncertainties were correlated to heterogeneity indices (HIs) calculated for each treatment field (38% < R² < 50%). A NTCP increase of more than 10% (absolute) was observed for less than 2.9% (anatomy-based positioning) and 1.2% (fiducial-based positioning) of the studied OARs and patient shifts. For target volumes TCP decreases by more than 10% (absolute) occurred in less than 2.2% of the considered treatment scenarios for anatomy-based patient positioning and were nonexistent for fiducial-based patient positioning. EUD changes for target volumes were up to 35% (anatomy-based positioning) and 16% (fiducial-based positioning).

Conclusions: The influence of patient positioning uncertainties on proton range in therapy of small lesions in the human brain as well as target and OAR dosimetry were studied. Observed range uncertainties were correlated with HIs. The clinical practice of using multiple fields with smeared compensators while avoiding distal OAR sparing is considered to be safe. © 2014 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4892601]

Key words: proton radiotherapy, proton range uncertainties, patient positioning

1. INTRODUCTION

Deviations of patient positions in radiotherapy occur between the patient position at the acquisition of a computed tomography (CT) image acquired for radiotherapy planning and patient setup position(s) for delivery of the (fractionated) treatment. Uncertainties in reproducing the patient position for delivery of irradiation are generally accounted for by the addition of a margin to any clinical target volume (CTV). The thereby created planning target volume (PTV) is used for treatment planning and shall increase the probability of appropriate dose delivery to the CTV taking into account patient setup uncertainties. It is essential to reduce healthy tissue irradiation for a patient treatment, keeping the margins added to a CTV as small as possible while achieving a favorable actual dose delivery to the CTV during treatment.

Additionally to the creation of a PTV for treatment planning, in proton therapy a range overshoot is applied to account for proton range uncertainties (i.e., errors in dose delivery and/or dose calculation). The range overshoot applied at the Francis H. Burr proton therapy center of the Massachusetts General Hospital (MGH) is 1 mm and 3.5% of the most distal proton range. Additional margins are applied for specific geometrical scenarios [e.g., lung or complex geometries (interfaces) in the head].

Several in vivo dose verification approaches are currently under development to allow monitoring actual dose delivery during and/or after proton therapy treatment. Patient setup uncertainties in particle therapy are recognized as major...
The current study aims to quantify the effects of patient setup errors on proton range as well as organ at risk (OAR) dose and target dose variations, specifically in cranial and head and neck locations due to smaller treatment fields and close proximity of OAR to targets. Patient positioning at the MGH is carried out using two different approaches, both based on orthogonal planar x-ray imaging before treatment. X-ray images are matched with digitally reconstructed radiographs considering either patient anatomical landmarks or previously implanted fiducial markers. While patient positioning uncertainties for both methods can be deduced from x-ray imaging before each treatment fraction, the resulting differences in dose distribution due to these uncertainties require a full recalculation of dose distributions taking into account shifted and/or rotated patient positions.

A quantitative analysis of the effect of patient setup position errors on proton range changes is carried out in the current study. Additionally the correlation of observed range uncertainties with heterogeneity indices calculated for each proton treatment field was investigated. By considering patients treated with small fields for malignancies in the head and neck region we were able to base our analysis on treatment plans delivered to patients at the MGH during the past year. To our knowledge this contribution of patient setup errors to proton range uncertainties was not quantitatively studied before.

Furthermore, the contribution of patient positioning errors on patient treatment outcome related parameters as equivalent uniform dose (EUD), normal tissue complication probabilities (NTCPs), tumor control probabilities (TCPs), and dose-volume histograms (DVHs) was studied for 10 target volumes and 35 OARs. Previous studies investigating organ motion and patient setup error contributions to dose parameters in prostate cancer treatments were published by Refs. 7–9. We did focus on small lesions because they are expected to show a more pronounced impact of the stated setup errors.

2. METHODOLOGY

2.A. Selection of clinical treatment plans

Proton treatment plans of patients irradiated with small fields in the head and neck region were selected for analysis. Treatment fields with nominal proton ranges in water between 75 and 173 mm were considered. The beam diameters were between 2 and 12 cm with most of the diameters being between 2 and 5 cm. An overview of the most important treatment parameters for all the patients included in this study is given in Table 1. All considered treatment plans were delivered by passive scattering in one of the two gantry treatment rooms available at the MGH. In total 38 treatment fields of 8 patients were considered. The total target doses of the considered fields were between 10.8 and 70.2 Gy[RBE] for each patient. Prescribed target doses may deviate from these considered field doses since fields with blocks and stereotactic treatment fields were excluded from this study.

2.B. Patient positioning uncertainties

Patient positioning uncertainties were considered for three linear patient translations, left-right, superior–inferior, and anterior–posterior as well as for three patient rotations, pitch about the left–right axis, roll about the superior–inferior axis, and yaw about the anterior–posterior axis. The single uncertainties for all considered degrees of freedom in positioning were acquired as follows. Prior to every field treated at the Francis H. Burr Proton Therapy Center (FHBPTC), dual, orthogonal images are acquired to measure the patient positioning variation during the treatment fraction using a Digital Imaging Positioning System (DIPS) software.13,14 When the patient has implanted fiducials, the DIPS software performs a ray backprojection 2D/3D alignment optimization. Without fiducials, the DIPS software performs a 2D/2D alignment optimization based upon user defined anatomical landmarks. Landmarks were selected to be in regions of high contrast and representative of the directional measurement. They include the base of the skull and top of the skull for superior/inferior alignment, left and right skull edges for left/right alignment, the front and back of the skull, the hard palate, the vertical and horizontal sella edges, right and left mastoids, median orbit edges, and the septum. The shifts generated by the DIPS software are applied prior to every treatment field to account for patient intrafractional motion and gantry isocenter sag. Since the anatomical landmarks are manually identified and depend upon user and window/level adjustments, the DIPS software suggested patient shifts and rotations include uncertainties. We retrospectively assessed the patient positioning uncertainty of the DIPS software using a preclinical open source 2D/3D automatic registration software (Reg23), which was previously validated with virtual data and clinical proton radiotherapy data.15,16 The Reg23 software performs an iterative 2D/3D registration optimization using a bone level mask. A registration accuracy of less than 0.73 mm and 0.18° was demonstrated by comparison to CBCT 3D/3D registration.15 In this study, we used the Reg23 rigid registration results as the ground-truth patient positions to calculate the mean and standard deviation of positioning errors of the DIPS software. Table II shows the standard deviations calculated from 14 patients and 432 fractions we analyzed. Matching of fiducial markers allows patient positioning with a higher accuracy compared over anatomy-based matching.

2.C. Dose calculation

In radiotherapy, Monte Carlo dose calculations are considered to provide the most accurate dose calculation.10 Within this work the Geant4-based (Ref. 11) Monte Carlo code package TOPAS (Ref. 12) was employed for all dose calculations. Monte Carlo dose calculations were assumed to be the baseline for the range analysis to remove uncertainties of
TABLE I. Patient and proton therapy treatment plan characteristics.

| Case no. | Age (years) | Gender | Treatment site | Diagnosis          | Total dose of considered proton fields (Gy[RBE]) | No. of fractions | No. of beam | Proton beam range/modulation in water (mm) | BEV area with dose > 70% of the maximum field dose (cm²) |
|----------|-------------|--------|----------------|--------------------|-------------------------------------------------|------------------|------------|------------------------------------------|--------------------------------------------------|
| 1        | 51          | Male   | Sella          | Pituitary adenoma  | 15.0                                             | 1                | 1          | 166/31                                   | 5.6                                               |
|          |             |        |                |                    |                                                 |                  |            | 102/25                                   | 6.4                                               |
|          |             |        |                |                    |                                                 |                  |            | 109/25                                   | 6.2                                               |
| 2        | 54          | Female | Left orbit     | Meningioma         | 10.8                                             | 5                | 1          | 153/27                                   | 5.5                                               |
|          |             |        |                |                    |                                                 |                  |            | 78/26                                    | 6.3                                               |
|          |             |        |                |                    |                                                 |                  |            | 114/24                                   | 6.9                                               |
| 3        | 49          | Female | Right cav sinus| Meningioma         | 43.2                                             | 24               | 1          | 115/46                                   | 24.1                                              |
|          |             |        |                |                    |                                                 |                  |            | 145/56                                   | 22.6                                              |
|          |             |        |                |                    |                                                 |                  |            | 119/52                                   | 24.4                                              |
|          |             |        |                |                    |                                                 |                  |            | 140/53                                   | 24.0                                              |
| 4        | 61          | Male   | Left acoustic  | Acoustic neuroma   | 50.4                                             | 28               | 1          | 130/27                                   | 6.9                                               |
|          |             |        |                |                    |                                                 |                  |            | 101/30                                   | 5.2                                               |
|          |             |        |                |                    |                                                 |                  |            | 134/25                                   | 7.3                                               |
| 5        | 37          | Female | Left orbit     | Hemangiopericytoma | 59.4                                             | 33               | 1          | 155/55                                   | 11.0                                              |
|          |             |        |                |                    |                                                 |                  |            | 75/45                                    | 13.4                                              |
| 6        | 33          | Female | Sinonasal      | Esthesioneuroblastoma | 70.2                                           | 39               | 1          | 128/110                                  | 48.9                                              |
|          |             |        |                |                    |                                                 |                  |            | 145/110                                  | 30.5                                              |
|          |             |        |                |                    |                                                 |                  |            | 78/32                                    | 26.7                                              |
|          |             |        |                |                    |                                                 |                  |            | 142/110                                  | 33.4                                              |
|          |             |        |                |                    |                                                 |                  |            | 81/45                                    | 19.4                                              |
|          |             |        |                |                    |                                                 |                  |            | 136/114                                  | 44.0                                              |
|          |             |        |                |                    |                                                 |                  |            | 96/50                                    | 20.9                                              |
|          |             |        |                |                    |                                                 |                  |            | 146/88                                   | 16.7                                              |
|          |             |        |                |                    |                                                 |                  |            | 95/69                                    | 17.4                                              |
|          |             |        |                |                    |                                                 |                  |            | 96/75                                    | 22.3                                              |
| 7        | 33          | Female | Sinonasal      | Adenoid cystic carcinoma | 62.0                                          | 31               | 1          | 173/84                                   | 53.3                                              |
|          |             |        |                |                    |                                                 |                  |            | 151/100                                  | 44.5                                              |
|          |             |        |                |                    |                                                 |                  |            | 151/109                                  | 46.5                                              |
|          |             |        |                |                    |                                                 |                  |            | 173/84                                   | 48.4                                              |
|          |             |        |                |                    |                                                 |                  |            | 160/92                                   | 25.5                                              |
|          |             |        |                |                    |                                                 |                  |            | 117/59                                   | 12.6                                              |
|          |             |        |                |                    |                                                 |                  |            | 143/94                                   | 26.6                                              |
|          |             |        |                |                    |                                                 |                  |            | 117/56                                   | 11.0                                              |
| 8        | 52          | Female | Base of skull  | Chondrosarcoma     | 60.0                                             | 30               | 1          | 135/58                                   | 20.5                                              |
|          |             |        |                |                    |                                                 |                  |            | 99/44                                    | 24.1                                              |
|          |             |        |                |                    |                                                 |                  |            | 146/51                                   | 22.4                                              |
|          |             |        |                |                    |                                                 |                  |            | 168/71                                   | 17.4                                              |
|          |             |        |                |                    |                                                 |                  |            | 131/46                                   | 13.7                                              |

TABLE II. Patient setup positioning uncertainties (1σ) at the Francis H. Burr proton therapy center of the MGH.

| Patient positioning coordinate | Positioning uncertainty (mm/deg) |
|---------------------------------|----------------------------------|
|                                 | Fiducial-based patient positioning | Anatomy-based patient positioning |
| Left/right                      | 0.74                             | 1.12                              |
| Superior/inferior               | 0.73                             | 1.57                              |
| Anterior/posterior              | 0.85                             | 1.18                              |
| Pitch                           | 0.64                             | 1.02                              |
| Roll                            | 0.55                             | 1.64                              |
| Yaw                             | 0.39                             | 0.89                              |

For each field, dose distributions were calculated for the planned patient position and for 36 shifted and rotated patient positions (18 each for anatomy- and fiducial-based patient positioning). The latter represent clinical patient setup errors observed at the MGH (Table II). While the number of 18 considered patient positions per positioning method appeared to cover a suitable number of scenarios, it also allowed reasonable computing times for Monte Carlo simulations. The positioning uncertainty values stated in Table II were combined to create worst case positioning scenarios for patients. Out of the 2ⁿ (64) possible combinations of 1σ uncertainties...
For this purpose the 50% and 90% dose falloff positions calculations were investigated (18 offset positions for each investigated separately for each beam such that 1368 dose ratios in both positive and negative directions corresponding to gated patient positions are combinations of shifts and rotations: For example, for fiducial-based patient positioning: +0.74 mm left, +0.73 mm superior, −0.85 mm anterior, −0.64° pitch, +0.55° roll, and +0.39° yaw). Dose calculations were carried out assuming the patient receives all fractions of the treatment in one of these 36 patient positions. This assumption is justified since systematic positioning errors were observed in clinical practice. The dose calculation grid applied for clinical treatment planning was also applied for Monte Carlo dose calculation, typically being of a resolution of 1.25 × 1.25 × 1.25 mm³. Dose distributions and CT data were rotated by the couch and gantry angles of the specific treatments applying linear interpolation in three dimensions to match the beam direction with one of the data coordinate axes. This facilitated further analysis.

### 2.D. Proton dose range analysis

The patient shift-induced proton range changes were investigated separately for each beam such that 1368 dose calculations were investigated (18 offset positions for each of 38 treatment fields for two patient alignment scenarios). For this purpose the 50% and 90% dose falloff positions \( r_i \) along each voxel line \( i \) in the beam’s eye view (BEV) were calculated for the full beam cross section of each beam and each patient position. For the calculation of this falloff position the maximum dose in the respective voxel line was considered. Dose falloff positions \( r_i \) were then linearly interpolated between the two adjacent voxels along the beam direction to allow a more accurate range analysis. Only areas in the BEV of the treatment fields with a dose above 70% of the maximum field dose \( (5 \times 10^{-7}) \) of all voxels with the highest doses were skipped for this maximum definition to ignore single voxel hot spots from Monte Carlo simulation were considered for range analysis. This threshold was selected to ensure the inclusion of cold spot areas during the appearance of hot spots in the target areas. At the same time it limits the analysis to the targets and excludes areas receiving significantly less than the planned dose. The dose falloff positions \( r_i \) for the dose distributions calculated for the patient at the planning position \( r_{plan} \) and at the shifted and rotated positions \( r_{shift} \) were then compared voxel line by voxel line in the BEV. The range difference \( d_{shift} \) for each voxel line \( i \) in the BEV was defined as the distance of the falloff position in the dose distribution calculated for the patient in planning position and the falloff position in the dose distribution calculated for a shifted and rotated patient position, \( d_{shift} = r_{shift} - r_{plan} \). In total, 38 proton treatment fields were analyzed. For each beam and each patient shift the mean range difference \( d_{shift}(beam) = \left( \frac{1}{n} \right) \sum_{i\in BEV} d_{shift}(i) \), averaged over the full BEV fulfilling, the 70% of the field maximum dose requirement \( (n \text{ voxels lines}) \), and its standard deviation \( \sigma(d_{shift}(beam)) \) were calculated as well as the maximum and minimum range deviations, \( d_{shift_{max}}(beam) = \max(d_{shift}, i \in BEV) \) and \( d_{shift_{min}}(beam) = \min(d_{shift}, i \in BEV) \). An overview of the variables used for proton dose range calculations is given in Table III.

### 2.E. Calculation of heterogeneity indices

For each proton treatment field in the planned patient position heterogeneity indices \( H_i \) were calculated according to Ref. 17. The heterogeneity index definition of Pflugfelder is for pencil beams only. It is defined as stated in Eq. (1). Multiple heterogeneity indices for passive scattering fields were calculated by heterogeneity index calculation of multiple pencil beams, applying a pencil beam spacing of 2 mm and a pencil beam radius of 2 mm (1σ). Throughout the treatment field fulfilling the 70% of the maximum field dose requirement: 

\[
H_i = \sqrt{\frac{\sum_{j \in S_i} \Phi_i(x_j, y_j, P_z) [\text{WED}_i(x_j, y_j, 0) - \text{WED}_i(0, 0, 0)]^2}{\sum_{j \in S_i} \Phi_i(x_j, y_j, P_z)}},
\]

where \( \Phi_i(x_j, y_j, P_z) \) therein represents the particle fluence of the considered pencil beam \( i \) at the considered discrete positions \( x_j, y_j, P_z \) within \( S_i \). The area \( S_i \) in the BEV was chosen to cover 4σ of the respective pencil beam radius. \( \text{WED}_i(x_j, y_j, 0) \) and \( \text{WED}_i(0, 0, 0) \) represent the water equivalent depths calculated from the patient surface to the 70% central pencil beam dose falloff depth at the positions \( x_j \) and \( y_j \) of the pencil beam center, respectively. With this definition a pencil beam in a homogenous phantom yields \( H_i = 0 \). The heterogeneity index parameterizes the complexity of the geometry, i.e., a
large value suggests a geometry that is less forgiving with respect to setup uncertainties. For a more detailed description of the considered heterogeneity index see Ref. 17. Heterogeneity index calculations were carried out at full spatial resolution of the computer tomography (CT) dataset used for treatment planning. For further considerations the mean $H_{\text{mean}}$, median $H_{\text{median}}$, and maximum heterogeneity index $H_{\text{max}}$ of each treatment field were calculated from the heterogeneity indices $H_i$ of the single pencil beams within the respective treatment field.

2.F. DVH, EUD, NTCP, and EUD analysis

An analysis of the DVHs of the clinical target volumes and organs at risk was carried out utilizing the CERR toolkit.18 Furthermore, the EUD changes as well as the NTCP and TCP changes were calculated according to Ref. 19. For target volumes additionally the fraction of the volume receiving the prescribed dose of the considered treatment fields as well as mean, minimum, and maximum dose changes were calculated.

3. RESULTS

3.A. Proton dose range analysis

Proton dose range evaluation was carried out for each beam and each shifted and rotated patient position. Results for a selected range evaluation (at 50% dose falloff) and patient positioning method (fiducial-based) are shown in Fig. 1.

![Fig. 1. Mean ($d_{\text{shift}}(\text{beam})$, green circles, error bars represent 1σ standard deviation (a)), minimum ($d_{\text{shift}}(\text{beam})$, blue triangles (b)) and maximum ($d_{\text{shift}}(\text{beam})$, red diamonds (b)) range differences at 50% dose falloff due to patient positioning uncertainties. The range differences in the beam’s eye view are shown for 38 proton treatment fields (arranged along the abscissa, separated by vertical lines). Each treatment field was analyzed for 18 different patient positions (arranged along the abscissa between the respective vertical lines of the considered treatment field). Shifts and rotations applied to the patient positions are according to the uncertainties observed for fiducial-based patient positioning at the MGH.](image-url)
Table IV. Median, maximum, and minimum (considering 18 shifted and rotated patient positions for each patient positioning method and range evaluation criterion) of the mean proton range differences $d_{\text{shift}}$(beam) distribution of clinical proton beams due to patient positioning uncertainties.

| Dose falloff position used for range evaluation (%) | Median($d_{\text{shift}}$(beam))(mm) | Minimum($d_{\text{shift}}$(beam))(mm) | Maximum($d_{\text{shift}}$(beam))(mm) |
|--------------------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
|                                                  | Fiducial-based patient positioning    | Anatomy-based patient positioning     | Fiducial-based patient positioning    |
|                                                  | Fiducial-based patient positioning    | Anatomy-based patient positioning     | Fiducial-based patient positioning    |
| 50                                               | 0.0                                  | −0.1                                 | 3.5                                  |
|                                                  | 0.5                                  | 0.5                                  | 6.1                                  |
|                                                  | −4.0                                 | −6.3                                 | 7.6                                  |
|                                                  | −5.4                                 | −12.7                                | 12.5                                 |

Shown are range difference quantities for all 38 beams (separated by vertical lines) and all shifts and rotations belonging to this selected patient positioning method (for a specific beam within two vertical lines).

An overview of the calculated mean proton range differences $d_{\text{shift}}$(beam) and their standard deviations $\sigma(d_{\text{shift}}$(beam))) for all patients and beams considered is presented in Tables IV and V. The maximum value of the 684 mean proton range differences (considering all beams, patient shifts and rotations) $\max(d_{\text{shift}}$(beam))) at the 50% dose falloff position was 6.1 mm for anatomy-based patient positioning. Fiducial-based patient positioning reduces this maximum mean range difference to 3.5 mm. For the 90% dose falloff position these values were 12.5 and 7.6 mm, respectively. The median (considering all patient shifts and rotations of one patient positioning method for all beams) $d_{\text{shift}}$(beam) was calculated to be less than 0.5 mm for all evaluation criteria and patient positioning methods. This indicates no trend toward over- or undershoot due to patient positioning errors.

The median (considering all beams) 1σ standard deviations of the mean range differences, $\sigma(d_{\text{shift}}$(beam))) for range evaluations of anatomy- and fiducial-based patient positioning are 2.8 and 1.6 mm (50% dose falloff) as well as 7.2 and 5.8 mm (90% dose falloff). The maximum and minimum (considering all beams) standard deviations of the mean range differences, $\max(\sigma(d_{\text{shift}}$(beam))) and $\min(\sigma(d_{\text{shift}}$(beam))) at 50% dose falloff were calculated to be 9.4 and 0.5 mm for anatomy-based patient positioning and 14.1 and 0.3 mm for fiducial-based patient positioning. These maximum and minimum standard deviations at 90% dose falloff were 32.4 and 0.8 mm for anatomy-based patient positioning and 21.1 and 0.6 mm for fiducial-based patient positioning.

No distinct linear correlation between the median and maximum (considering all patient shifts and rotations of one patient positioning method for a single beam) standard deviations of the mean range differences $\sigma(d_{\text{shift}}$(beam))) and the planned proton beam range in water was observed. Calculated coefficients of determination $R^2$ (equaling the square of the Pearson correlation coefficient for the applied linear least square regression analysis) were less than 18% for maximum (considering all patient shifts and rotations of one patient positioning method for a single beam) standard deviations, $\max(\sigma(d_{\text{shift}}$(beam))) and planned proton beam range, and less than 9% for median (considering all patient shifts and rotations of one patient positioning method for a single beam) standard deviations $\min(\sigma(d_{\text{shift}}$(beam))) and planned proton beam range. These values did not depend on whether anatomy- or fiducial-based patient positioning was considered (Fig. 2). A value of $R^2$ equaling 1 would mean that all seen range deviations can be contributed to the planned proton beam range, whereas a $R^2$ of 0 means that there would be no correlation between the two.

A correlation was identified when considering the median (considering all patient shifts and rotations of one patient positioning method for a single beam) standard deviations $\min(\sigma(d_{\text{shift}}$(beam))) and mean heterogeneity index $H_{\text{mean}}$ (of the respective treatment field (coefficients of determination $R^2$ were larger than 43% for anatomy-based patient positioning and larger than 38% for fiducial-based patient positioning). This correlation is more than two times stronger than the observed correlation to the nominal beam ranges. The determination coefficients $R^2$ for the correlation of maximum (considering all patient shifts and rotations of one patient positioning method for a single beam) standard deviations $\max(\sigma(d_{\text{shift}}$(beam))) and mean/median/maximum heterogeneity indices $H_{\text{mean}}/H_{\text{median}}/H_{\text{max}}$ were similar to the correlations of the median standard deviations $\min(\sigma(d_{\text{shift}}$(beam)))) (Fig. 3 and Table VI).

Table V. Median, maximum, and minimum (considering 18 shifted and rotated patient positions for each patient positioning method and range evaluation criterion) of $\sigma$ standard deviations of the mean proton range differences $\sigma(d_{\text{shift}}$(beam))) distribution of clinical proton beams due to patient positioning uncertainties.

| Dose falloff position used for range evaluation (%) | Median($\sigma(d_{\text{shift}}$(beam))) (mm) | Minimum($\sigma(d_{\text{shift}}$(beam))) (mm) | Maximum($\sigma(d_{\text{shift}}$(beam))) (mm) |
|--------------------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
|                                                  | Fiducial-based patient positioning    | Anatomy-based patient positioning     | Fiducial-based patient positioning    |
|                                                  | Fiducial-based patient positioning    | Anatomy-based patient positioning     | Fiducial-based patient positioning    |
| 50                                               | 1.6                                  | 2.8                                  | 14.1                                  |
|                                                  | 5.8                                  | 7.2                                  | 21.1                                  |
| 90                                               | 0.3                                  | 0.5                                  | 9.4                                   |
|                                                  | 0.6                                  | 0.8                                  | 32.4                                  |

Medical Physics, Vol. 41, No. 9, September 2014
3.B. DVH, EUD, TCP, and NTCP analysis

The DVHs of the organs at risk and the target volumes were evaluated individually. Dose shifts in the cumulative DVHs for OARs in the order of up to 20% toward higher and lower doses could be observed. Two selected examples of such changes in the DVH are shown in Fig. 4. A quantitative evaluation of the dose distributions for the organs at risk (OAR) and the target volumes was carried out by calculating the relative changes in the EUDs due to shifts and rotations in the patient positions for each region of interest. This analysis assumes that all fractions of the dose are delivered in one patient position. Table VII summarizes the observed changes in the EUD for the OAR as well as the target volumes of the patients included in this study. For the target volumes a maximal decrease in the EUD of 35% (anatomy-based patient positioning) and 16% (fiducial-based patient positioning) were calculated. For target volumes, the maximum reduction in the volume receiving the prescribed field doses was 82% (anatomy-based patient positioning) and 51% (fiducial-based patient positioning), respectively.

For the patients included in this study the analysis of NTCPs for relevant organs at risk showed that most of the considered treatment scenarios (>85%) resulted in absolute NTCP changes below 1%. A rather low number of patient shifts however showed considerable changes in the NTCP. For anatomy-based patient positioning 18 out of 630 (<2.9%) considered shifts showed an NTCP increase of more than 10% (absolute), for fiducial-based patient positioning 7 cases (<1.2%) showed an increase of this extent.
NTCP increase observed was 75% (absolute). Figure 5 shows mean dose, maximum dose, and EUD for each simulated patient shift and rotation for all OARs included in this study. The vertical lines separate different OARs. Quantities for different patient shifts and rotations for the same organ at risk are shown between two vertical lines. The figure clearly shows that variations in these parameters are considerably different for different OARs. In general, larger variations were seen for OARs which were adjacent or close to target volumes.

For target volumes a TCP decrease of more than 10% (absolute) was observed for 4 shifts out of 190 shifts investigated (<2.2%) for anatomy-based patient positioning. No such decrease was observed for fiducial-based patient positioning shifts. The maximum TCP decrease observed for anatomy-based patient positioning was 14% (absolute) and 5% (absolute) for fiducial-based patient positioning. Variations in mean, minimum, and maximum dose as well as in EUD and in the volume receiving the prescribed dose were calculated for the target volumes considered and are shown in Fig. 6 for fiducial-based patient positioning. Variations of these parameters tend to be smaller for treatments applying a higher number of fields.
TABLE VI. Coefficients of determination $R^2$ for the correlation of median and maximum standard deviations of mean range differences $d_{\text{shift}}(\text{beam})$ and mean, median, and maximum heterogeneity indices $H_{\text{mean}}$, $H_{\text{median}}$, and $H_{\text{max}}$ for 38 proton treatment fields. Mean and maximum standard deviations were calculated considering 18 shifted and rotated patient positions for each category (anatomy- and fiducial-based patient positioning as well as range evaluation at 90% and 50% dose falloff position).

| Coefficient of determination $R^2$ (%) | Median heterogeneity indices $H_{\text{median}}$ | Mean heterogeneity indices $H_{\text{mean}}$ | Maximum heterogeneity indices $H_{\text{max}}$ |
|---------------------------------------|----------------------------------------------|---------------------------------------------|---------------------------------------------|
|                                       | Fiducial-based patient positioning            | Fiducial-based patient positioning            | Fiducial-based patient positioning            |
| Median($\sigma(d_{\text{shift}}(\text{beam})))$ (90% falloff evaluation) | 33                                           | 45                                          | 45                                          |
| Maximum($\sigma(d_{\text{shift}}(\text{beam})))$ (90% falloff evaluation)   | 28                                           | 38                                          | 37                                          |
| Median($\sigma(d_{\text{shift}}(\text{beam})))$ (50% falloff evaluation)   | 33                                           | 38                                          | 44                                          |
| Maximum($\sigma(d_{\text{shift}}(\text{beam})))$ (50% falloff evaluation) | 9                                            | 14                                          | 23                                          |

4. SUMMARY AND DISCUSSION

4.A. Proton dose range analysis

The direct impact of patient positioning uncertainties on proton dose range was studied. The proton range changes of small clinical treatment fields were quantitatively investigated for two patient positioning approaches at the MGH proton therapy facility. Patient positioning errors were found to introduce considerable proton range changes in the order of several millimeters. Maximum mean proton range changes of up to 12.5 mm were observed. It could be shown that the range changes introduced by setup errors of anatomy-based patient positioning can be substantially reduced by fiducial-based patient positioning. For example, $1\sigma$ proton range uncertainties of 2.8 mm at the 50% dose falloff position can thereby be reduced to 1.6 mm. The observed reduction of the proton dose range uncertainties for patient positioning with fiducial markers in general supports the effort taken to make patient positioning more precise.

Typically the nominal proton beam range is used in clinical recipes to account for range uncertainties. However, no strong correlation between patient positioning uncertainty-induced proton dose range changes and the planned proton beam nominal range were seen. In contrast to this finding 38%–50% of the observed range uncertainties could be allocated to heterogeneity indices. This suggests the use of heterogeneity indices for clinical beam angle optimization procedures and margin recipes.

4.B. DVH, EUD, TCP, and NTCP analysis

For less than 2.9% (anatomy-based patient positioning) and 1.2% (fiducial-based patient positioning) of the considered patient shifts and rotations a NTCP increase of more than 10% (absolute) was observed for OARs. For more than 85% of the considered OARs and patient shifts the NTCP increase was less than 1% (absolute). For target volumes TCP decreases larger than 10% (absolute) occurred in less than 2.2% of the considered treatment scenarios for anatomy-based patient positioning and were nonexistent for
fiducial-based patient positioning. EUD changes were up to 35% for target volumes.

Thus the reduction of proton range uncertainties by more precise patient positioning was generally confirmed by the quantitative investigation of the previously stated clinical plan evaluation parameters EUD, NTCP, and TCP. The variations of these parameters however also revealed a strong dependence on the actual clinical treatment situation.

The analysis of clinical outcome parameters furthermore allowed to study the appropriateness of strategies to compensate uncertainties in proton treatment delivery (e.g., compensator smearing and use of margins in treatment planning). These strategies typically address different contributing uncertainties at the same time and are targeting not only patient positioning uncertainties. This study investigated the influence of patient positioning uncertainties only. It assumes delivery of all dose fractions in one patient position to assess the full impact of setup uncertainties even down to the single fraction limit. Based on the previously stated NTCP and TCP parameters the clinical practice of using multiple

| Parameter/patient positioning                      | Median Fiducial-based | Median Anatomy-based | Standard deviation Fiducial-based | Standard deviation Anatomy-based | Minimum Fiducial-based | Minimum Anatomy-based | Maximum Fiducial-based | Maximum Anatomy-based |
|----------------------------------------------------|-----------------------|----------------------|----------------------------------|---------------------------------|------------------------|-----------------------|------------------------|-----------------------|
| Organs at risk                                     |                       |                      |                                  |                                 |                        |                       |                        |                       |
| Mean dose/mean dose (planning position)            | 1.00                  | 1.00                 | 0.11                             | 0.22                            | 0.60                   | 0.44                  | 1.64                   | 2.26                  |
| Maximum dose/maximum dose (planning position)      | 1.00                  | 1.00                 | 0.08                             | 0.15                            | 0.63                   | 0.39                  | 1.45                   | 1.81                  |
| EUD/EUD (planning position)                        | 1.00                  | 1.00                 | 0.12                             | 0.22                            | 0.53                   | 0.36                  | 1.78                   | 2.53                  |
| Target volumes                                     |                       |                      |                                  |                                 |                        |                       |                        |                       |
| Mean dose/mean dose (planning position)            | 1.00                  | 1.00                 | 0.00                             | 0.01                            | 0.98                   | 0.96                  | 1.01                   | 1.02                  |
| Minimum dose/minimum dose (planning position)      | 0.99                  | 0.98                 | 0.05                             | 0.09                            | 0.86                   | 0.72                  | 1.14                   | 1.25                  |
| Maximum dose/maximum dose (planning position)      | 1.00                  | 1.00                 | 0.01                             | 0.02                            | 0.98                   | 0.96                  | 1.05                   | 1.07                  |
| EUD/EUD (planning position)                        | 1.00                  | 1.00                 | 0.04                             | 0.08                            | 0.84                   | 0.65                  | 1.12                   | 1.18                  |
| Volume receiving prescribed dose/volume (planning position) | 1.00                  | 1.00                 | 0.30                             | 0.44                            | 0.49                   | 0.18                  | 2.01                   | 3.50                  |

**Fig. 5.** Changes in mean (green circles), maximum (red diamonds), and equivalent uniform (EUD, blue crosses) dose in OARs due to patient setup uncertainties observed for fiducial-based patient positioning at the MGH. For each of the 35 OARs the changes due to 18 different patient shifts and rotations are shown. The data for different OARs are arranged along the abscissa and separated by vertical lines. The dose parameters for different patient shifts are plotted between these vertical lines.
FIG. 6. Changes in mean [green circles (a)], minimum [blue diamonds (a)], maximum [red triangles (a)], and equivalent uniform [EUD, blue crosses (a)] dose in target volumes due to patient setup uncertainties observed for fiducial-based patient positioning at the MGH. The changes in the volume receiving the prescribed dose are shown as orange circles (b). For each target the changes due to 18 different patient shifts and rotations are shown. The data for different target volumes are arranged along the abscissa and separated by vertical lines. The dose parameters for different patient shifts are plotted between these vertical lines.

fields with smeared compensators while avoiding distal OAR sparing is considered to be safe. Other uncertainties as interfractional setup variations, anatomical changes, or organ motion might further contribute or wash out the effects of errors in patient setup.

5. CONCLUSIONS

The presented study allows to separately judge the influence of patient positioning uncertainties in proton therapy of small lesions in the human brain on proton range directly as well as on clinical treatment plan parameters. It contributes to a quantitative understanding of this important component within the context of more general range uncertainties in proton therapy and justifies efforts taken to make patient positioning more precise. The finding that the strategies currently applied at the MGH Francis H. Burr Proton Therapy Center to cope with proton dose range uncertainties, i.e., the use of multiple fields with smeared compensators while avoiding distal OAR sparing, are appropriate is of highest clinical significance.
ACKNOWLEDGMENTS

Stephen Dowdell, Drosoula Giantsoudi, Clemens Grassberger, Maryam Moteabbed, Jan Schümann, Mauro Testa, and Joost Verburg contributed in fruitful discussions. Marta Bueno participated in discussing the calculation of a heterogeneity index for the proton fields investigated in this work. J.L. was supported by a scholarship of the Rectorate of the University of Vienna.